Assessment of graded changes in the Central Nervous System, during general anaesthesia and surgery in man, using the auditory evoked response

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ABSTRACT

The thesis examines the use of the auditory evoked response (AER) to measure 'depth of anaesthesia'.

The historical background to general anaesthesia is reviewed. Developments in recording the evoked responses with particular reference to the auditory evoked response and the factors which influence this are described.

The effects of increasing concentrations of six general anaesthetic agents (halothane, enflurane, isoflurane, etomidate, Althesin and propofol) on the brainstem and early cortical auditory evoked responses and the modification of these effects by surgical stimulation were investigated. The AER as an indicator of 'awareness' was also assessed.

These studies showed that all six general anaesthetics produced qualitatively similar changes in the early cortical section of the AER. These were increases in latency and reductions in amplitude of the waves Pa and Nb with increasing concentrations of anaesthetics. The amplitude changes were partially reversed during surgery.

Only the inhalation anaesthetics (halothane, enflurane and isoflurane) produced changes in the brainstem response. The latencies of waves III and V and their interpeak intervals increased with increasing anaesthetic concentrations. These changes were not reversed during surgery.

The latency of the early cortical wave Nb, emerged as a possible indicator of 'awareness' in that, in a group of patients anaesthetised with nitrous oxide and oxygen prior to general surgery, latencies below 44.5 ms were associated with a positive response using the isolated forearm technique. In a second study,

during Caesarian section surgery, latencies below 44.5 ms occurred more frequently following delivery in patients in whom anaesthesia was maintained with nitrous oxide-opiate anaesthesia only, compared to those to whom an enflurane supplement was given.

These findings and their theoretical implications are examined in the light of the literature. The practical application of the technique as a clinical monitor of anaesthetic depth is discussed.

CONTENTS

INDEX OF ABBREVIATIONS

AER	auditory evoked response
cv	coefficient of variation
dB	decibels
ED_{50}	effective dose for 50% of patients (see 12.2.3.)
EEG	electroencephalogram
EOG	electrooculogram
FM	frequency modulated
GLC	gas liquid chromatography
HPLC	high performance liquid chromatography
i.v.	intravenous
MAC	minimum alveolar concentration (see 2.6.)
S.D.	standard deviation
SER	somatosensory evoked response

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CHAPTER 1

INTRODUCTION

This project was started following Professor Gareth Jones' suggestion that evoked responses might be used to measure 'depth of anaesthesia'. The concept of 'depth of anaesthesia' implies a relationship between the concentration of an anaesthetic agent and its effect on central nervous system (CNS) function. The latter is far from easy to quantify and it may be surprising that, 170 years after the discovery of anaesthetics there is no graded effect on the CNS which can be used to measure reliably the 'depth of anaesthesia'.

The administration of anaesthetics has been likened to driving a car in the dark without headlights, the driver knows how hard he is putting his foot on the accelerator but not how fast the car is going. Likewise the anaesthetist knows how much anaesthetic he is giving but not how deeply anaesthetised is the patient. Although the anaesthetist can rely on the fact that giving more anaesthetic will make the patient deeper, and giving less will make the patient lighter he does not know the absolute amount of anaesthetic required to produce a particular 'depth of anaesthesia' in a particular patient. Individual sensitivity is, of course, a feature of all drugs, but with general anaesthetics the consequences of inappropriate dosage are particularly disturbing. Too much anaesthetic may lead to severe side effects such as circulatory and respiratory depression and prolonged recovery time. Not enough can result in a patient being aware of, i.e. hearing or feeling, the surgical procedures.

The most graphical description of awareness during anaesthesia is given in an editorial in the British Journal of Anaesthesia (Editorial, 1979) by a doctor having a Caesarian section. She reports:- "I instantly understood my predicament: that I was lying there, intubated, covered in green towels, my abdomen split open, strange people delving inside me..... My first

reaction to this was an irrational surge of fear and panic and a desperate necessity to move..... The closest parallel I can think of is being in a coffin, having been buried alive." She continues "I remained in this state of mind (horizontal and supine) but otherwise totally dissociated, without any body image; continuously filled with fear, listening to every word, every sound in the theatre, quite compos mentis and fully appreciating my position."..... Following delivery when she heard the baby crying then she says "There followed a confusion of sound and half-heard words. I am sure I didn't lose any of my consciousness I just didn't seem to manage to catch what the nurses were saying."..

- Not only was she completely aware of the situation but she was also in considerable pain which she describes "there came three rough stripes across my abdomen.....This was the first pain I had felt..... It was bad from the onset, and it increased in severity. In character it was exceedingly unpleasant.... Searing, melting, pressing me into the table... I could not stand the pain a split second longer. I tried to roll about (useless). From then on I absolutely and totally gave up....I did not go unconscious; the pain did not stop. From then onwards there is a long period of amnesia until I woke up in bed in the ward."

The problem is that there is no gold standard for measuring 'depth of anaesthesia' or even an agreed definition of the term anaesthesia. However, surgery does require the anaesthetist to provide 3 things for his patient:-

1) ***Unconsciousness*** or at least lack of awareness of surgical procedures.

2) ***Control of reflex responses to surgery*** It is important that the patient does not move in response to surgical procedures and that their autonomic responses, such as changes in blood pressure, heart rate and respiration rate are kept within reasonable limits.

3) ***Muscular relaxation*** This is necessary to permit surgical access for certain operations and, when required, to allow mechanical ventilation.

Prior to the 1950's it was necessary to give a large dose of general anaesthetic to produce the required degree of muscular relaxation to permit surgery. These amounts were almost always in excess of those needed to produce unconsciousness. A number of dangerous side effects resulted, the most significant of which were the depression of the respiratory and cardiovascular systems and prolongation of recovery time.

The introduction of a separate class of drugs to produce muscular relaxation was in most respects a spectacular advance. These neuromuscular blockers were specific in their action, they did not affect the CNS, and their effects were readily reversed. Only a light level of general anaesthesia was then needed to render the patient unconscious thus reducing side effects and ensuring a quick recovery. But if the anaesthetist inadvertently gave too little general anaesthetic for that particular individual the patient could awaken during the operation but be unable to communicate this situation in any way.

Traditionally the anaesthetist had used clinical signs of the reflex responses to surgical stimulation to indicate the patient's 'depth of anaesthesia'. However, neuromuscular blockers, by paralysing the skeletal muscles, obscured the most useful clinical signs of 'depth of anaesthesia', namely movement in response to surgical incision and changes in respiratory pattern. The remaining signs, which were changes in blood pressure, heart rate, pupil size, sweating and tears, are unreliable because these variables are controlled by autonomic factors and different anaesthetics and other drugs used during anaesthesia affect this system to different degrees. Pre-operative medication, induction agents, patient age, general health, site and extent of surgical stimulation, body temperature and duration of anaesthesia all modify the relationship between these signs and 'depth of anaesthesia'.

To give an example, if a change in blood pressure is used as a guide to 'depth of anaesthesia' it should vary predictably with dose of anaesthetic. Cullen and co-workers in 1972 studied

groups of anaesthetised patients under closely controlled conditions. In the first hour of anaesthesia there was a relationship between blood pressure and anaesthetic dose for some anaesthetics but this disappeared with prolonged anaesthesia.

To judge 'depth of anaesthesia' the anaesthetist needs a signal that :-

a) is unaffected by neuromuscular blocking drugs,

b) indicates whether the patient is awake or not,

c) if the patient is unconscious, shows graded changes with changes in anaesthetic concentration,

d) shows similar graded changes with all general anaesthetic drugs,

e) shows appropriate changes with surgical stimulation.

The electro-encephalogram (EEG) was an obvious signal to explore. Being generated by the CNS it is not affected by neuromuscular blockers and it reflects the changes in naturally occurring sleep. Graded changes in both unprocessed and processed EEG signals with increasing general anaesthetic concentration have been reported for a range of general anaesthetics (this topic is reviewed in **Section A**) but so far no index has emerged that changes in the same way with all general anaesthetics.

Evoked responses are an extension of EEG techniques. These are changes in the EEG pattern as a result of either auditory, visual or somatosensory stimulation and are extracted from the background noise by computer averaging. Being neurogenic in origin they are also not affected by neuromuscular blockers. The averaged evoked response consists of a series of waves which represent the electrical activity passing along the pathways of that modality.

The ***auditory evoked response (AER)*** was specifically chosen for investigation in this thesis because it furnishes 15 waves covering the entire neuroaxis from cochlear nucleus to frontal cortex and the anatomical origins of these waves have been extensively studied. As the site of activity of anaesthetics is unevenly distributed within the CNS (Davis et al. 1984, 1986) it seemed likely that at least one part of the evoked response would be

affected in a graded manner by anaesthetic agents. The auditory evoked response has the added advantage that a click stimulus given through headphones is a very acceptable stimulus in the operating theatre environment. In contrast, the anatomical origins of the somatosensory evoked response are less clear and this signal provides fewer (4-6) waves from medulla to frontal cortex (Desmedt & Cheron 1980). The visual evoked response has no easily measurable subcortical components (Harding & Rubinstein 1980).

The reticence on the part of anaesthetists in clearly defining 'depth of anaesthesia' means that variables with which to correlate the changes in the evoked response had to be generated. Deepening of anaesthesia follows changes in anaesthetic concentration so step-wise changes in anaesthetic concentration were applied and the AER was examined for graded changes. To ensure that the technique could be applied when a range of different anaesthetics was employed, six general anaesthetic agents of diverse chemical structures were examined.

Changing the concentration is not the only way of changing depth of anaesthesia, which is sometimes viewed as a balance between the depression of the CNS due to drugs and the stimulation by sensory events such as surgery. The changes in the AER brought about by anaesthetic drugs were therefore examined to see if they were reversed by surgical stimulation.

An important question is "what is the relationship between changes in the AER and loss of consciousness?" It would seem a comparatively easy matter to look for changes in the AER related to the transition from awake to unconscious. However, in anaesthetic practice large doses of potent fast acting drugs are used to take the patient's state rapidly from awake to unconscious and the transition is too fast to monitor. If this transition is effected slowly then there is often too much muscle activity to obtain a reasonable record. In an attempt to resolve this situation the AER was recorded in patients who had been given neuromuscular blocking drugs and where clinical practice has indicated that a high incidence of awareness would be expected e.g. following induction of anaesthesia or during Caesarian section.

The layout of the thesis is as follows:-

Chapter 1 Introduction

Section A Literature review

Chapter 2 Historical development in anaesthesia, the agents, the adjuncts and the methods of assessing 'depth of anaesthesia'.

Chapter 3 Historical background to the evoked response.

Chapter 4 Factors which affect the auditory evoked response.

Section B Methods

Chapters 5, 6 and 7 Design of studies, anaesthetic protocols, estimations of anaesthetic concentration. Evoked potential recordings and analysis.

Section C Results

Chapter 8 Effects of general anaesthetics on the AER.

Chapter 9 Effect of surgical stimulation on the AER.

Chapter 10 An AER indicator of awareness.

Section D Discussion

Chapter 11 Discussion of the findings of the thesis.

Chapter 12 Significance of the findings and their contribution to the field.

SECTION A

LITERATURE REVIEW

CHAPTER 2

HISTORICAL DEVELOPMENTS IN ANAESTHESIA

2.1. *Early anaesthesia*

The use of potions to relieve pain and produce unconsciousness predates historic records. Most ancient civilizations discovered alcohol before they discovered 'writing'. References to wine 'irep' appear in Egyptian text around 2600 BC and references to beer 'henket' a hundred or so years later (Nunn 1989). Alcoholic beverages were familiar to Greeks and Romans. It is not known how long the poppy and herbs such as hyoscyamus and mandragora have been used. Seed capsules of Papaver somniferum (the opium poppy) have been found in Egyptian tombs dating from 1500 BC.

Surgery *was* undertaken in 'classical times'. It ranged from simple procedures such as opening of abscesses and removal of simple tumours, recorded in the 2nd and 3rd millennia BC, to more complex and painful procedures in the 2nd century AD (Retsas 1986). However, Egyptian medical records and the Hippocratic writings do not appear to consider pain relief when they refer to operative intervention (Breasted 1930). This is perhaps not so surprising considering that as recently as 1770 the British Navy did not think to recommend pain relief for limb amputation in their detailed instructions to surgeons (Lloyd and Coulter 1958). Even though the drugs were available, the extent to which they were used to produce pain relief and unconsciousness during surgery is not well understood. As far back as 5 BC there are records of the Roman surgeon, Celsus, using a concoction probably of hyoscyamus and opium to relieve toothache and to provide a sleepy forgetful patient for his surgery (Spencer 1935). There is also evidence from Roman (Bostock and Riley 1861) and Greek (Gunther 1934; Apuleius 1481) writings of the use of mandrogora for pain relief of surgery in the 1st century AD.

2.2. *Modern anaesthesia*

In the Western world, no real attempt was made to relieve the pain of surgery until the 19th century. Wells started to use nitrous oxide for routine dental extraction in 1844 (Gwathmey and Baskerville 1918). This was over 70 years after the discovery of the gas by Priestley, in Leeds in 1772 (Duncum 1947) and almost 50 years after Davy (1800) published his researches suggesting the use of this gas for analgesia in minor surgery.

It was the demonstration of ether anaesthesia by Morton in 1846 (Anaesthetics Antient and Modern 1907) which established clinical anaesthesia and changed the face of surgery for all time. Faraday had recognised its potential as an anaesthetic in 1818 (Anaesthetics Antient and Modern 1907). It was actually discovered by Valerius Cordus as far back as 1540 (Duncum 1947). Chloroform was introduced into anaesthetic practice by Simpson in 1847 (Anaesthetics Antient and Modern 1907) and when in 1848 he overcame religious opposition it was used routinely by him in obstetric practice. In the same way that other ether derivatives such as divinyl ether, isopropyl methyl ether etc. followed the established clinical use of diethylether, so other chlorinated hydrocarbons such as ethyl chloride and chloroethylene, followed chloroform.

The routine use of electro-cautery led to the screening of fluorinated compounds for non-inflammable agents. Of these fluoroxene was the first to be used clinically in 1955 (Orth & Dornette 1955; Sadove et al. 1956) but this was soon eclipsed by the introduction of halothane in 1956 (Johnstone 1956). The ether derivatives enflurane in 1966 (Virtue 1966) and isoflurane in 1971 (Dobkin et al. 1971) have been added to the list of fluorinated compounds in the as yet unfulfilled search for the ideal anaesthetic.

2.3. *Tracheal intubation*

Technology had not stood still throughout this period. Coincident with the introduction of ether into clinical practice, Snow in 1847 developed a "regulating ether inhaler" which allowed the percentage of ether in air to be controlled. This is the

precursor of the modern vaporizer. In the same year he modified it for use with chloroform. The development for routine clinical use of the technique of tracheal intubation was also an advance, although the impact that this would have on anaesthetic practice was not realised at the time. Although, in fact, intubation was first demonstrated to the Royal Society by Hook in 1667, Magill is considered to be the father of endotracheal anaesthesia. The introduction (Jackson 1913) and widespread use of Jackson's laryngoscope reduced the uncertainty, inaccuracy and trauma of blind intubation which must have aided Magill and Rowbotham's (Rowbotham & Magill 1921) enthusiastic pioneering of this technique considerably. Introduction of reliable mechanical ventilation then paved the way for the use of neuromuscular blocking drugs.

2.4. *Neuromuscular blockers*

In the 16th century news of curare reached Europe from the New World where the Indians had been using it for poison arrow tips (Feldman 1973). In 1942 Griffiths and Johnston administered 5ml of a curare preparation to a patient undergoing appendicectomy and thus initiated the greatest single advance in anaesthetic practice in recent times.

Brodie (1811,1812) had already shown at the beginning of the 19th. century that curare did not kill provided artificial ventilation was maintained until the animal recovered spontaneous respiratory effort, i.e. death due to curare being due to primary cessation of ventilation. In 1851, Claude Bernard demonstrated in a series of studies that the drug acted by paralysing transmission from motor nerve to muscle, sensory nerve conduction and spinal cord action being unaffected. Classification of curare on the basis of what later turned out to be impurities was carried out by Boehm in 1886. In 1935 King isolated pure curare and in 1940 Gill prepared Intocostrin, the form in which Griffiths and Johnston introduced it into anaesthetic practice. Although there was controversy about its safety, finally Gray and his co-workers (Gray & Halton 1946) in Liverpool pioneered the use of the 'pure technique' using nitrous oxide and oxygen with supportive artificial ventilation thus making the use of neuromuscular block

in anaesthesia safe. Had the technique of artificial ventilation not already been well established in anaesthetic practice, introduction of neuromuscular blockers into anaesthesia might have been less smooth.

2.5. *Intravenous agents*

The introduction of hypodermic syringes into anaesthetic practice by Pravaz and Wood (Duncum 1947) independently during the years 1851-3 paved the way for intravenous (i.v.) anaesthesia. Although Christopher Wren had used a goose quill with a bladder attached to give a intravenous injection of morphine as early as 1656 (Morgan 1987). With the syringe available for routine clinical use a number of compounds, mainly barbiturates, were used intravenously to produce anaesthesia. The most significant advance in this area was the introduction by Lundy and Tovell in 1934 of sodium thiopentone, still the most widely used intravenous induction agent.

Total intravenous anaesthesia, i.e. anaesthesia induced and maintained using i.v. agents alone, has long been a goal in anaesthetic practice. With the introduction of the steroid anaesthetics in 1955 following the report of hydroxidione, by Laubach, P'an and Rudel, this seemed a possibility at last. Althesin was the last of this group to be introduced (Child et al. 1971; Campbell et al. 1971) but it was withdrawn from the market in 1984 because of its allergenic properties. Ketamine, a phencyclidine derivative, has enjoyed limited popularity as an induction agent and then mainly in children. It was introduced into clinical practice by Domino, Chodoff and Corsen in 1965. The use of etomidate, an imadazole, as an anaesthetic was pioneered by Janssen Pharmaceutica (Janssen et al. 1971) and first used in man in 1973 (Doenicke et al. 1973). Its suppression of adrenal cortical function led to its withdrawal as an agent for continuous infusion in 1984 leaving the anaesthetist without a "total intravenous anaesthetic agent". The most promising candidate for this role is now di-isopropylphenol or Propofol. This was shown to have anaesthetic properties in patients by Kay and Rolly in 1977. At that time it was solubilized in Cremophor EL, however, it has more recently been introduced in an aqueous emulsion of soya bean oil under the trade name Diprivan (Imperial Chemical Industries).

2.6. *Clinical signs of 'depth of anaesthesia'*

In 1847, Snow's book on 'The inhalation of the vapour of ether' was published. It was visionary in at least two respects:-

1) It described a vaporizer to regulate the amount of ether administered.

2) It subdivided anaesthesia into 5 stages on the basis of a series of clinical signs, such as changes in respiration, eyeball activity, pupil size, reflex activity.

The first stage or degree was when the patient was conscious of his surroundings and able to direct his voluntary movement. In the second stage both these aspects of function were present but diminished. The entry to stage 3 indicated that a patient was ready for surgery. In this stage there was no evidence of mental function and consequently no voluntary movement but there were muscular contractions in response to extraneous events, and respiration continued. In the fourth stage there were only respiratory movements and patients did not respond to external events. The fifth stage was considered to be critical for the patient. In this stage the respiratory muscles were paralysed or feeble. Snow had learnt for how long a certain concentration had to be given to reach a particular stage of anaesthesia and conversely, for how long the anaesthetic had to be switched off for the patient to move back to the previous stage. This "balancing of several particulars", to use Snow's own words, to assess 'depth of anaesthesia' is still the basis of modern anaesthetic practice.

Guedel in 1937 further advanced the assessment of depth of anaesthesia by categorizing the signs of ether anaesthesia to indicate the readiness for different types of surgery. He divided anaesthesia into 4 stages based on changes in respiration, presence of eyeball activity, pupil size, and the times when the eyelid reflex or reflex swallowing or vomiting were likely to occur (Fig.2.1). According to Guedel's classification:-

Stage 1 beginning of induction to loss of consciousness.

Stage 2 delirium.

Stage 3 surgical stage, divided into 4 planes.

Stage 4 began with respiratory paralysis and ended with cardiac failure and death.

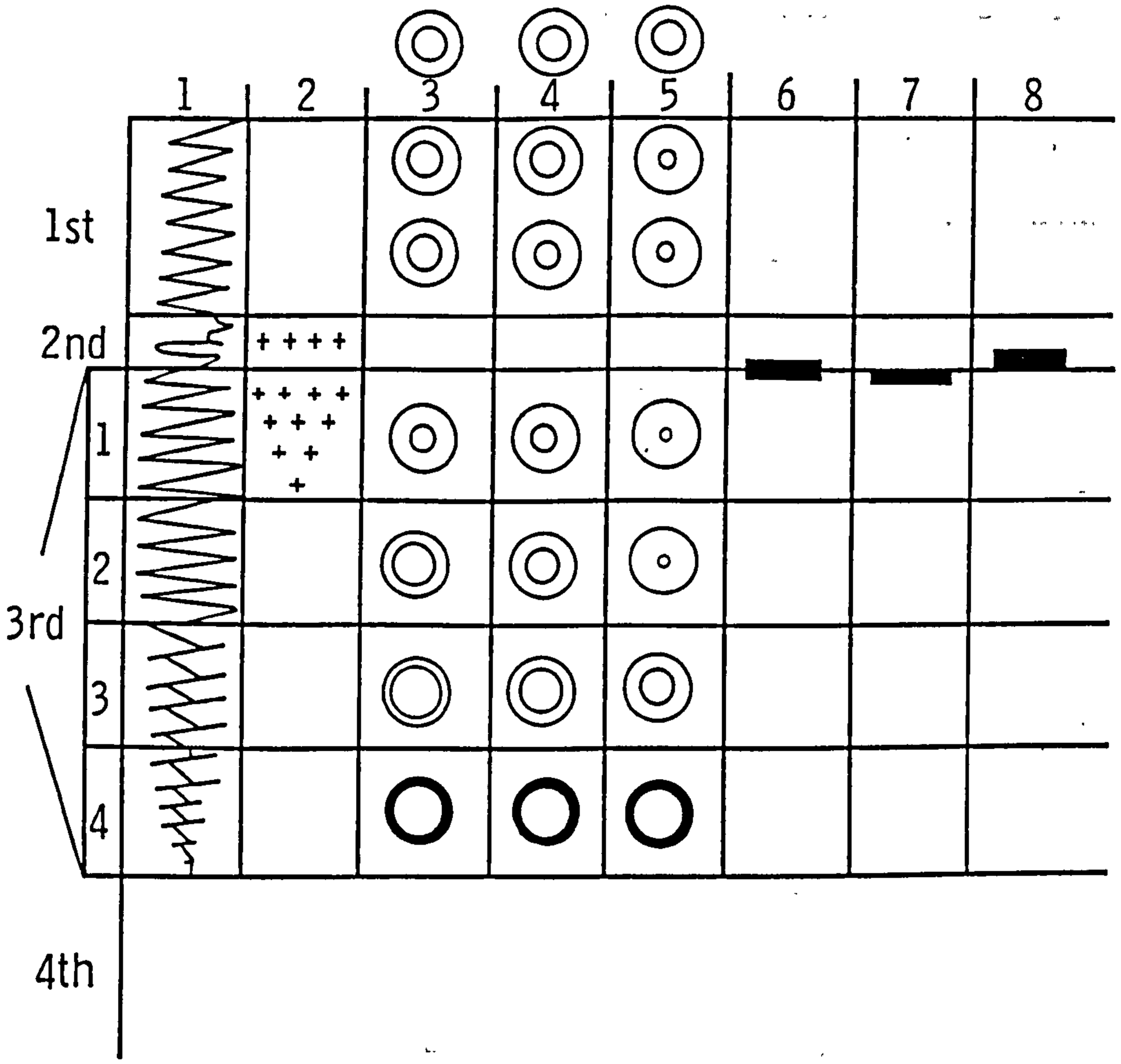


Fig.2.1. The signs of anesthesia. (Taken from Guedel A.E., 1937. Inhalation Anesthesia - a fundamental guide. MacMillan, New York.)

Column 1 - Respiration (tidal volume and rate)

Column 2 - Eyeball activity (presence)

Column 3 - Pupil size (without pre-anaesthetic medication)

Column 4 - Pupil size (with morphine & atropine as pre-anaesthetic medication)

Column 5 - Pupil size (with morphine as pre-anaesthetic medication)

Column 6 - Eyelid reflex (presence ▬)

Column 7 - Time when swallowing may occur (▬)

Column 8 - Time when vomiting may occur (▬).

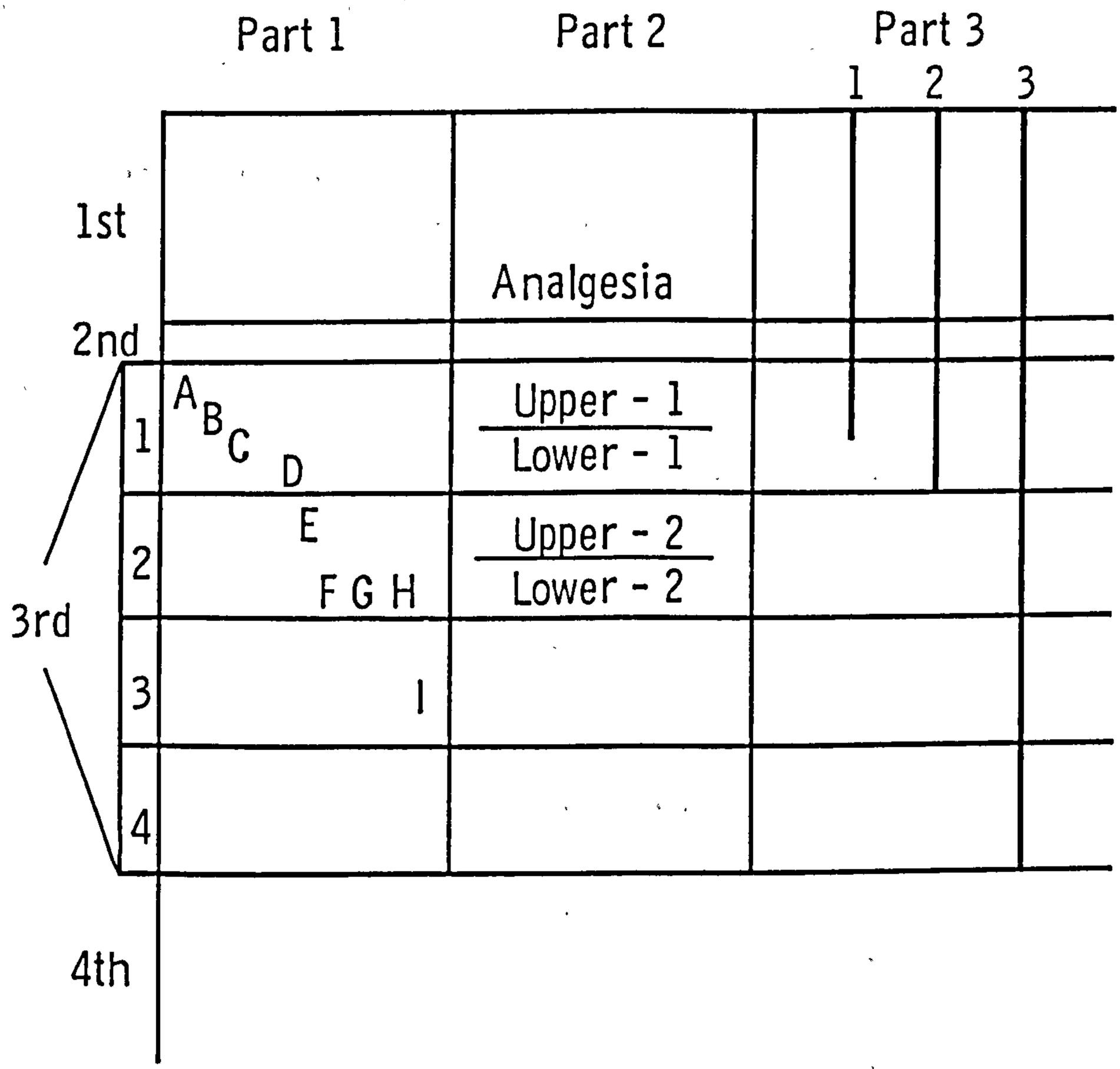


Fig.2.2. Stages of anesthesia to control certain reflex responses. (Taken from Guedel A.E., 1937. Inhalation anesthesia - a fundamental guide. MacMillan, New York.)

Part 1. Depth of anesthesia required for control of surgical reflexes. (A=fibrous coverings and ligamentous attachments of bone, brain, glandular tissue, kidney, spleen, liver, stomach, intestine and B=skin, C=posterior pharyngeal reflex, D=nerve, E=laryngeal reflex - cough reflex, F=muscle, G=traction reflex, H=sub-diaphragmatic reflex, I= smooth muscle tone.)

Part 2. Depth of anesthesia required for various surgical procedures.

Part 3. Potency of various anesthetic agents. 1=nitrous oxide, 2=ethylene, 3=ether, chloroform, divinyl oxide and cyclopropane.

Guedel's stage 3 corresponded to Snow's Stages 3 and 4 and Guedel's stage 4 to Snow's stage 5. Certain stages had to be reached to control various reflex responses so that certain types of surgery could be performed (Fig.2.2). Although fairly reliable for ether anaesthesia, these signs were less reliable for the other inhalational agents such as ethylene, chloroform and cyclopropane.

The introduction of neuromuscular blocking agents was of great value in anaesthetic practice in that abdominal surgery, which at one time would have required deep anaesthesia, could now be carried out at a much lighter plane. However, their use created problems in the assessment of 'depth of anaesthesia'. Seven out of nine of Guedel's signs involved skeletal muscle activity and the remaining components, pupil size and tear secretion were, in isolation, of limited value.

The administration of intravenous agents by continuous infusion also raised problems in the assessment of 'depth of anaesthesia'. Analyses of intermittent blood samples to estimate the effect of these drugs on the brain are clearly impractical and there is too much individual variation in the factors which affect the uptake and elimination of these drugs for a reliable estimate to be obtained from the infusion rate. With the inhalational agents reasonable estimates of brain concentration can be obtained with experience in precisely controlling the concentration of inspired gas. The anaesthetist is able to control both uptake and elimination of the inhalation agents, which takes place in the lungs, whereas with the intravenous anaesthetic agents only the uptake of the drug can be manipulated.

Further Eger (1974) introduced the concept a minimum alveolar concentration (MAC) which prevents movement in response to surgical incision in 50% of patients. This has been determined for all the inhalation agents and by direct measurement of the end-tidal concentration provides a guide as to the amount of anaesthetic which will ensure adequate anaesthesia.

In addition, autonomic signs such as changes in blood pressure, heart rate, vasoconstriction (Johnstone 1974) skin conductance (Goddard 1982) and the occurrence of sweating, which were hitherto

useful but never totally reliable indicators of depth with the inhalational agents, are of no value with these new intravenous agents. As a consequence, what constitutes an overdose for one patient may not adequately anaesthetised another.

In the presence of intravenous agents and neuromuscular blockers 'depth of anaesthesia' is therefore particularly difficult to assess. On account of the neuromuscular blockers, movement in response to surgical incision is no longer available as a sign of light anaesthesia. Neither are changes in respiration because the patient is being mechanically ventilated. This left the anaesthetist with the horrifying prospect that, without his knowledge, the patient may be paralysed - and unable to move but 'wide awake' throughout the entire operation. It therefore became important to find measures of depth of anaesthesia which were unaffected by neuromuscular blockers and the anti-cholinergic and anti-adrenergic drugs used during surgery, and which could be used for all anaesthetic agents. The electro-encephalogram (EEG) was an obvious candidate.

2.7. *Electroencephalographic indices of 'depth of anaesthesia'*

There are numerous studies on the effect of anaesthetic agents on the EEG. The report by Gibbs, Gibbs and Lennox in 1937 was probably the first of these although the most comprehensive of the earlier studies was that of Courtin, Bickford and Falconer in 1950. They described in detail the progressive changes in the EEG with nitrous oxide-oxygen-ether anaesthesia. These ranged from the low amplitude fast activity seen in the awake patient, through the gradual increase in amplitude and slowing of the frequency of the waves as anaesthesia deepens, to the complete suppression associated with respiratory failure (Fig.2.3). However, Galla, Rocco and Vandam in 1958 found little correlation between these levels and the traditional signs and stages of anaesthesia. Most workers report similar progressive changes in the EEG with increasing anaesthetic concentration, nevertheless the literature is confusing. The precise changes in the EEG attributed to a particular anaesthetic vary from laboratory to laboratory. Clark and Rosner (1973) suggest that this could be partly explained by the different combinations of anaesthetic agents used but

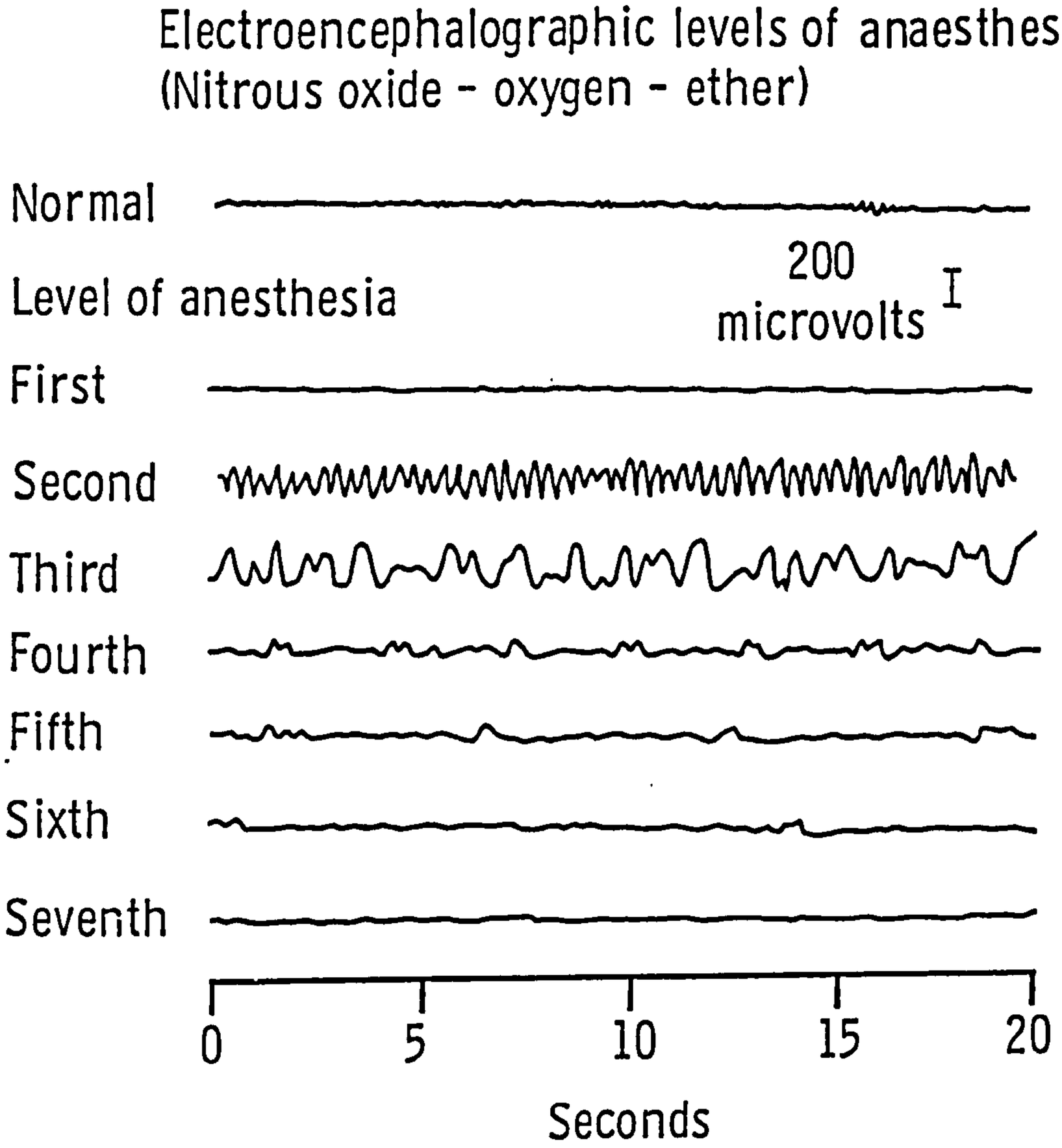


Fig.2.3. Progressive changes in the low frequency components of the electro-encephalogram (EEG) with nitrous oxide-oxygen-ether anaesthesia. (Taken from Courtin, Bickford and Faulconer, 1950. Staff meetings of Mayo Clinic.)

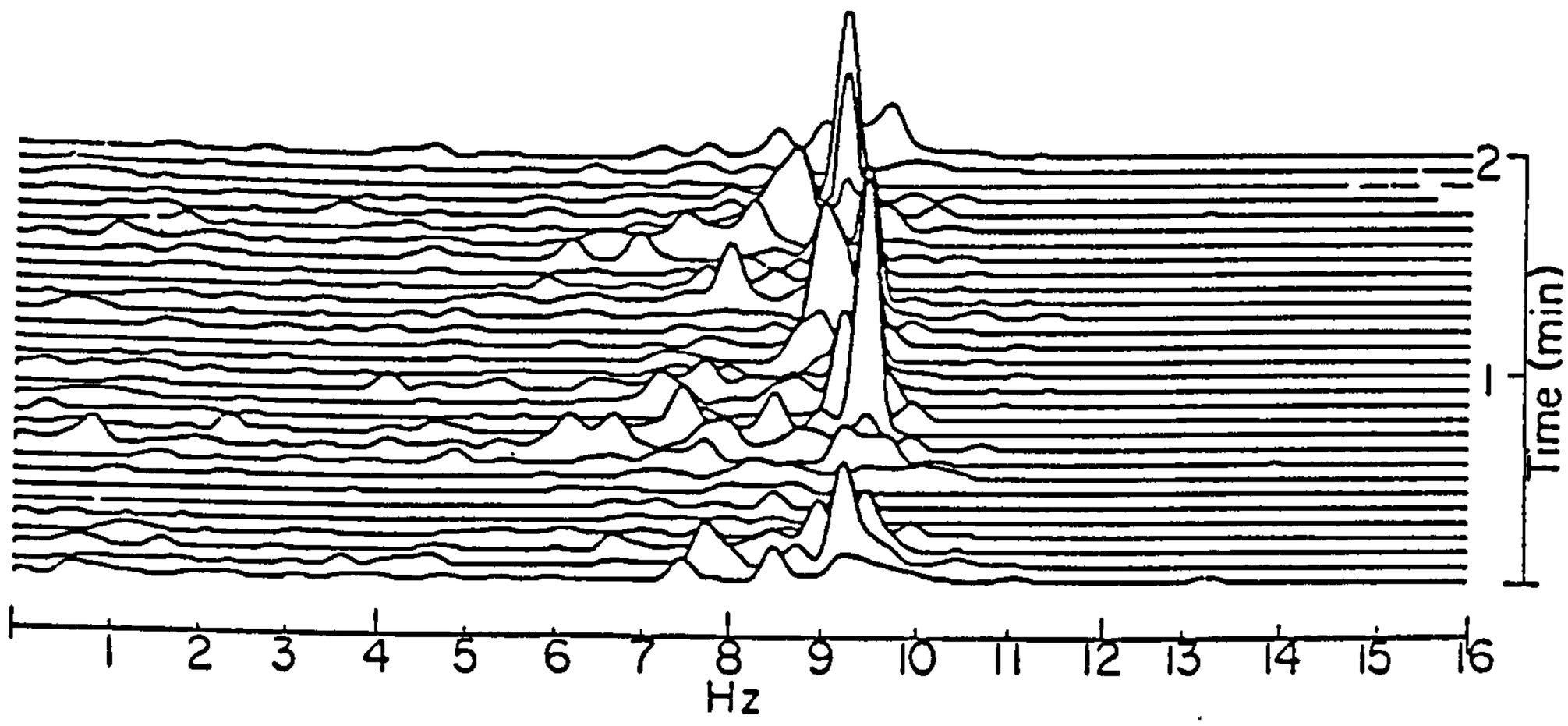


Fig 2.4. A compressed spectral array of the EEG. (Taken from Bickford, Billinger, Fleming and Stewart, 1972, Proceedings San Diego Biomedical Symposium.)

acknowledge that it also seems likely that different anaesthetic agents may have different effects on the EEG. This limits its use in anaesthetic practice but is perhaps not the most serious drawback. Clinical anaesthetists have been reluctant to use a technique where the data are so bulky and where the interpretation is subjective. Efforts have therefore been concentrated on processing the EEG to condense the information and simplify the display. This has met with some success for individual anaesthetics at least.

The frequency and amplitude components of the EEG have been the main targets. ***Power spectral analysis*** uses a fast Fourier transformation or zero crossing technique to calculate the contribution of each frequency to the EEG waveform. Consecutive power spectra can be presented with the overlap suppressed (Fig.2.4.) to give the ***compressed spectral array*** developed by Bickford, Billinger, Fleming & Stewart in 1972. Statistical methods have been applied to calculate the median of the frequency distribution by Stoeckel, Schwilden, Lauven & Schuttler (1981) or its 95th percentile which is in fact the ***spectral edge frequency*** by Rampil and his co-workers (1980). Amplitudes at different frequencies have been used by Volgesi (1978) to calculate an ***augmented delta quotient*** (that is a mean amplitude of delta frequencies divided by a mean amplitude of the entire EEG signal). Maynard in 1977 combined an analysis of the frequency content of the EEG with amplitude - weighted with respect to frequency to give the ***cerebral function analyzing monitor.*** This technique has the same disadvantage as the EEG for monitoring depth of anaesthesia, that is, that different anaesthetic drugs produce different changes. The cerebral function analyzing monitor has however, been found useful in long term monitoring situations, such as, in comatose patients where trends are more important than absolute values. A slightly different approach used by Gersh and co-workers (1980) involves pattern recognition using the Kullback-Leibler nearest neighbour rule. However, in spite of these attempts to process the EEG, a suitable index of depth of anaesthesia has yet to emerge.

CHAPTER 3

HISTORICAL BACKGROUND TO THE AUDITORY EVOKED RESPONSE

3.1. *The first electronic averager*

In response to an idea put forward by Hunt, Dawson (1951) produced the first electronic averager and in doing so revolutionised the field of evoked potential recording. Previous methods used superimposition of ink written or photographed traces but this did not allow more than 10-20 responses to be used. In 1961, Clark et al. produced the first digital averager which rapidly went into commercial production (Computer of average transients - C.A.T.). Further developments in averagers since that time have led to the present day multi-channel recorders which include powerful signal processing facilities.

3.2. *The late cortical response*

Davis and co-workers had first reported a response in the EEG to auditory stimuli in 1939. Williams and Graham in 1963 were the first to record this 'late' cortical auditory evoked response using electronic averaging and Davis and Yoshie (1963) a few months later published a clear account of the shape and latency of the response. Davis took the primary role in establishing the method clinically and in 1965 described the response as arising from a wide area of the cortex, like a cap worn well forward on the head. It is now generally agreed from studies in animals (Teas and Kiang 1964; David and Sohmer 1972) and man (Chatrain et al. 1960; Celesia et al. 1968; Lovrich et al. 1988) that waves which occur later than 50 ms are generated mainly by the frontal cortex and association areas (Fig.3.1.).

3.3. *The early cortical response*

By electronic averaging of the EEG in response to a click stimulus, Geisler, Frishkopf and Rosenblith (1958) picked out several

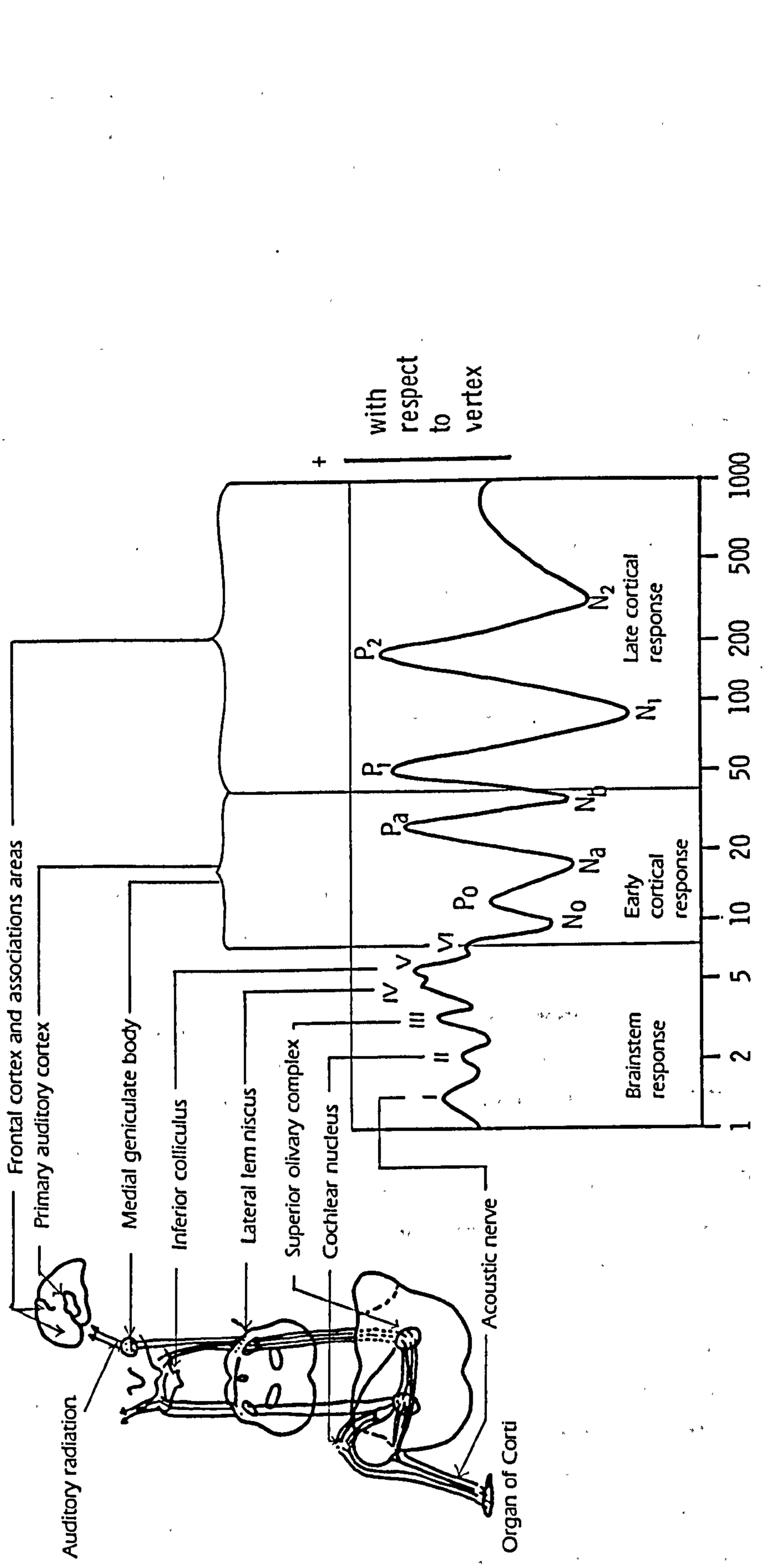


Fig.3.1. Origin of the auditory evoked response (AER). The AER consists of a series of waves generated from specific anatomical sites in the auditory pathway as the electrical activity passes from cochlea, through the brainstem, to the cortex.

potentials with onset latencies varying from 8-30 ms, which they believed to be of primary cortical origin. Subsequently Goldstein and Rodman (1967) labelled the waves occurring at 8-10, 10-13, 16-30, 30-45 and 40-60 ms as No, Po, Na, Pa, Nb respectively. Picton et al. (1974), on the basis on scalp topographical studies speculated that No, Po and Na might be generated from the medial geniculate and polysensory nuclei of the thalamus with Pa representing widespread activity of the polysensory cortex (Fig.3.1.). This is not so much an accepted view, as a compromise between the conflicting opinions in the literature.

Despite extensive brain mapping investigations in man and animals, coupled with investigations involving neuropathological lesions in man and experimentally produced lesions in animals, there is still considerable discussion concerning the origins of the early cortical waves. A number of specific questions need to be answered:-

3.3.1. Is the response myogenic or neurogenic?

3.3.2. Are Na and Pa seperately generated?

3.3.3. What are the generators of Na and Pa?

3.3.1 Is the response myogenic or neurogenic?

Contamination by evoked muscle responses which occur over the same time period as the early cortical waves has been the source of much controversy. Bickford et al. in (1963) produced evidence that the potentials described by Geisler were myogenic. He demonstrated that their amplitudes were increased by cervical muscle tension and that they could be abolished by curare. Several years of discussion and argument concerning the nature of these potentials followed. Cody et al. (1964) provided evidence that these potentials were myogenic and mediated by the vestibular system rather than the cochlea. He reported that patients who possessed a reduced or absent vestibular response to caloric stimulation also showed a significant reduction or absence of these potentials when the affected ear was stimulated acoustically. Also patients with a unilateral absence of hearing, but a normal response to caloric stimulation, yielded normal potentials. Ruhm et al. (1967) whilst accepting that myogenic potentials could be recorded in this time period were able to record potentials similar to those described

by Goldstein and Rodman (1967) in a patient with no semicircular canal function. Further they were able to record similar potentials to those recorded on the scalp directly from the temporal cortex. Finally, Harker et al. (1977) showed that when total muscle paralysis was produced by a suxamethonium infusion, clear early cortical potentials with peaks at the latencies described by Goldstein and Rodman (1967) were recorded. Similar potentials could be produced in non-paralysed subjects as long as they were relaxed. They attributed the findings of Bickford et al. (1963) to the small number of responses (n = 150) from which they derived their averages suggesting that many more stimuli are necessary before the smaller non-myogenic components can be clearly seperated from the ongoing noise.

More recently Yokoyama et al. (1987) have re-opened the controversy by claiming that No and Po are the remnants of the post-auricular response. Fig.3.2. is a reproduction of their data demonstrating that the post-auricular response persists even during light (diazepam-induced) sleep. Streletz et al. (1977) have also recorded the post-auricular response during light sleep in several subjects. This myogenic response first described by Kiang et al. in 1963 is thought to be derived from the reflex arc of the facial nerve pathways. It is particularly troublesome in contaminating mastoid recording but can also be a problem when recording from other parts of the scalp. Its most prominent deflections are within the 10-20 ms range, precisely the same time window as the No/Po/Na complex. In a tense subject the post-auricular response can obliterate the entire early cortical response.

Kavanagh et al. (1984) also believe that the wave Yokoyama et al. (1987) refer to is myogenic, however Kavanagh et al. refer to it as the P wave. They recommend this nomenclature to overcome the confusion resulting from the use of different low pass filter settings. Their data are reproduced in Fig. 3.3. They demonstrate that when the filter settings used to record the early cortical response (0-100Hz) are changed from those used to record the brainstem response (15-3000Hz), the section of the waveform between 5 and 12 ms changes from a -ve/+ve/-ve complex which in Fig. 3.3. is labelled SN/P/Na_2 to a -ve trough. This -ve trough is Goldstein and Rodman's (1967) Na. They believe that Goldstein and Rodman's Po

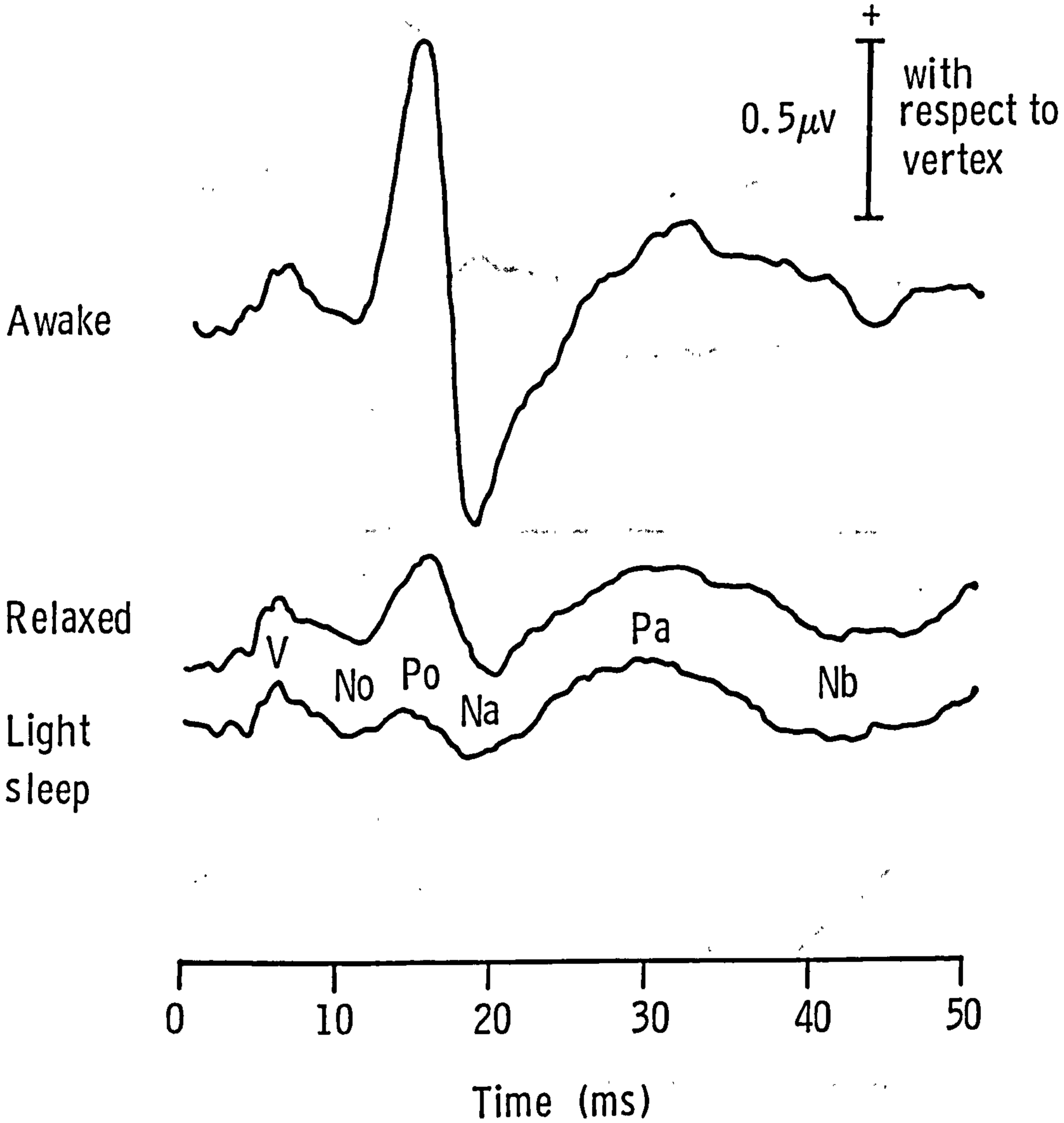


Fig.3.2. Auditory evoked response recorded sucessively from awake to light (diazepam - induced) sleep (after Yokoyama et al. 1987). The high biphasic wave (post-auricular muscle response) decreased in amplitude and disappeared when No and Po appeared in light sleep. Prominent distortion of Pa and Nb potentials occurred in the awake state.

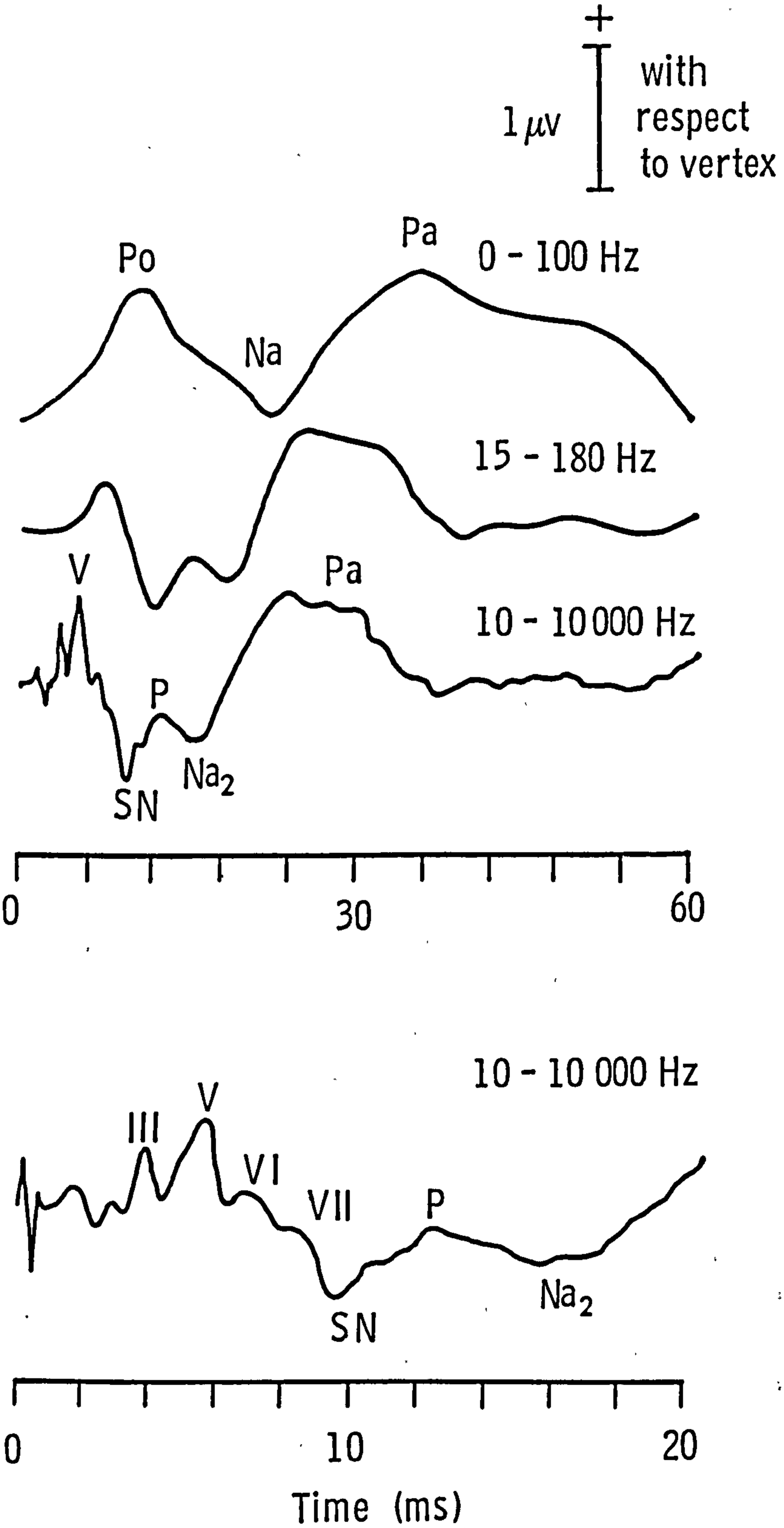


Fig.3.3. Method of classifying brainstem and early cortical responses proposed by Kavanagh et al. (1984). The early cortical response as recorded by Goldstein and Rodman (1967) is shown at the top of the diagram (filter band pass 0 - 100 Hz). The brainstem and early cortical response can be recorded simultaneously using a band pass of 10 - 10,000 Hz.

is actually a highly filtered brainstem response and that the P wave, which occurs at the same time as the post auricular response has a myogenic origin. It is clearly important when discussing the No/Po/Na complex to note whether Po follows a brainstem response, as in the data of Yokoyama et al. (they used a filter band pass from 10Hz - 1 KHz) or whether it is in place of the brainstem response as in the case of Goldstein and Rodman's.

Hashimoto (1982), based on scalp and intracranial recordings, attributes a neurogenic origin to No and Po. His recordings were made with a filter band-pass of 30-3000Hz and they show a clear brainstem response. He is refering to the SN and P waves described by Kavanagh et al. (1984). Taking care with muscle artefact rejection and using multiple intracranial recording sites, he traced large negative potentials from their maxima in the inferior colliculus of the brainstem to their maxima in the scalp. This midbrain origin is compatible with the wide scalp distribution of these waves, suggesting volume conduction from a deep generator source (Streletz et al. 1977).

3.3.2. Are Na and Pa seperately generated?

Various workers have used scalp topography to try and pin-point the generators of Na and Pa. In these studies a non-cephalic reference such as naso-pharyngeal or sterno-vertebral is prefered, as an active reference can contribute to the potential difference. As these are surface recordings, it is not possible to distinguish between surface and deep generators. However, on the basis of isopotential maps, models are constructed showing the orientation and location of dipoles which would produce such electric fields. In common with all modelling methods, a model is chosen which gives a reasonable fit to the data out of an infinite number of possibilities i.e. it is not a unique solution.

Deiber et al. (1988) provides evidence for distinct generators for Na and Pa by scalp mapping of responses to left and right ear stimulation. Na was picked up with maximal amplitude by frontal electrodes and decreased gradually towards the occipital regions. Pa culminated in fronto-central electrodes and decreased sharply in in amplitude towards parieto-occipital regions with potential reversal at occipital sites. Pa had a longer time course and was

more widely distributed than Na. The most striking difference between Na and Pa potential fields was the distribution of isopotential lines on the scalp, widespaced at Na latency and narrow spaced at Pa latency. This suggested to them that the generator could be more deeply situated for Na than for Pa. Scherg and Von Cramon (1986) using similar methodology had reported different conclusions. These workers suggested that both Na and Pa were related to bilateral activation of the auditory cortex. They used 2D modelling of responses recorded by a coronal line of electrodes, but this is unlikely to be the reason for the discrepancy as Deiber et al. (1988) found the potential gradients of Na and Pa were to be different even when using only electrodes disposed on a coronal plane. These workers propose that the filtering of low frequencies used for the modelling procedure could have been responsible. Scherg and Von Cramon used a 20 Hz high pass digital filter as opposed to their 1.6 Hz filter. When Deiber et al. applied 20 Hz high-pass to their data, there was no great difference between Na and Pa maximal gradients, whatever montage used.

Other support for functionally distinct generators for these two waves comes from their lateralization with respect to the stimulus. Woods and Clayworth (1985) found Na to be larger in amplitude and shorter in latency at electrodes contralateral to the stimulated ear in monaural conditions, but it showed no evidence of binaural occlusion. (Binaural occlusion occurs when the response to binaurally presented sounds are less than the sum of the responses to the constituent monaural inputs). In contrast Pa did not show contralateral shortening of latencies or amplitude enhancement but did demonstrate binaural occlusion.

Neuropathological investigations furnish further evidence for the seperate generation of Na and Pa. Responses of patients with unilateral temporal lobe lesions, in particular those involving the posterior aspects of the superior temporal gyrus, showed Pa amplitude to be reduced and the latency delayed in the damaged hemisphere whereas Na amplitude and latency were unaffected (Kraus et al. 1982; Kileny et al. 1987).

3.3.3. What are the generators of Na and Pa?

Deiber et al. (1988) propose a deep generator for Na. They suggest that this component could correspond to the large negative activity recorded at the level of the inferior colliculus by Hashimoto (1982). Celesia (1976) and Lee et al. (1984), using subdural electrodes placed on the surface of the auditory cortex, recorded a negativity peaking at the same latency range as the scalp component Na. It is the view of Deiber et al. that this does not necessarily imply a cortical origin for Na since subdurally recorded negativity can be picked up at a distance from a subcortical source. They speculate that polysynaptic activity originating from midbrain or diencephalic nuclei could account for the Na component

Despite the limitations of scalp mapping there is a certain amount of consistency in the conclusions concerning the generators of Pa. It is generally agreed that Pa is bilaterally generated by symetrically placed generators in the superior-temporal cortices. Wood and Wolpaw (1982) describe a positive maxima fronto-centrally at around 30ms and suggest a dipolar source in the primary auditory cortex on the superior temporal plane near the temporoparietal junction. Cohen (1982) found polarity reversal of Pa at the level of the Sylvian fissure, which taken with the steep voltage gradients over this region suggested a restricted dipole source in the superior temporal plane. Ozdamar and Kraus (1983) reported Pa amplitude to be largest at the vertex as compared to the temporal lobes and to be symetrical over the temporal lobes. Their data indicated that Pa reflected bi-electrical events processed equally by both hemispheres and they propose two equally active, vertically oriented dipole sources located about the temporal lobes. (Pa would be expected to be greatest at the midline (Cz) where the response of the two generators would sum.) Deiber et al. (1988) likewise suggest that Pa could be mainly related to the simultaneous activation of both superior-temporal auditory cortices and propose that at Pa maximal amplitude the configuration of the scalp electric field could result from the activity of two tangential dipoles, one in each temporal lobe, with positive poles oriented inwards. Scherg and Von Cramon (1986) proposed that during the Pa latency range, two dipolar source activities overlap in time, the main one being tangential and the secondary one radial.

Some workers have recorded directly from the cortex, i.e. Celesia et al. (1968) in man and Kaga et al. (1980) in cat. Both groups concluded that Pa is generated by the superior temporal gyrus (post ectosylvian gyrus or A1 in cat). Kaga et al. went even further and demonstrated by acute and chronic lesions in the cat that Pa was absent when the anterior portion of A1, contralateral to the stimulus was removed. Buchwald et al (1981), carried out similar studies to those of Kaga et al (1980) and confirmed their findings although they refer to the Pa analogue as wave 7. The work of these two groups is a very useful contribution as it demonstrates the correlation between scalp, cortical surface and intracranial recordings and precise brain lesions. These workers also address the question as to whether the cat is an appropiate model of the human early cortical response. The morphology of the cat and human early cortical response are similar although the latency of Pa is earlier in the cat. Both show the same changes in the waveform with increases in stimulus rate and intensity. However, the cat Pa is almost entirely contralateral. Both cat and human early cortical responses are unaffected by neuromuscular blocking drugs (Harker et al. 1977). Pa in the cat (Buchwald et al. 1981) as in humans (Celesia and Puletti 1971; Mendel and Hosick 1975) was shown to be relatively stable during barbiturate anaesthesia. In general the cat early cortical response seems to model the human response quite closely.

Support for the superior temporal origin of Pa comes from neuropatholgical investigations. Lee et al. (1984) recording from implanted chronic subdural electrodes from posterior banks of the sylvian fissure in epileptic patients reported that a potential corresponding in properties to the scalp recorded Pa, that is showing similar effects of binaural occlusion, intensity of stimulation and drugs, occurred on the superior temporal gyrus. Kraus et al. (1982) found that Pa was attenuated in temporal lobe lesions involving the para- and infra-ventricular regions of the cerebral cortex. Temporal lesions affecting primary and association auditory cortices and adjacent white matter thalamic projections appeared to produce asymetrical Pa distributions. Pa was smallest over the injured temporal lobe and was often larger over the intact hemisphere, regardless of the ear stimulated, than over the vertex confirming that the generator sites of Pa are essentially

bilateral. Kileny et al. (1987) found that lesions affecting the posterior half or two thirds of the temporal lobe tended to compromise the integrity of the Na-Pa complex recorded over the involved hemisphere. The superior temporal gyrus was affected in all such cases whereas in cortical lesions that did not include the temporal lobes the amplitude, configuration and the coronal distribution of the Na-Pa complex was intact. On the basis of the findings in 2 patients, with anterior temporal lobectomy and with normal early cortical responses, these workers further narrowed down the source of the neural generators of Na-Pa to the posterior aspect of the superior temporal gyrus and the sylvian fissure.

In summary, practically all the work mentioned so far points to the generators of Pa being in the region of the posterior superior temporal gyrus. In contrast to this others have found that destruction of this area does not affect Pa. Woods et al. (1987) showed that, in three of the five patients tested, early cortical responses were entirely normal despite extensive bilateral lesions of the auditory cortex. They therefore find no support from their data that Pa is generated exclusively in primary auditory cortex or auditory association areas. They believe it to be generated more caudally and that the results of previous studies which suggest that abnormalities in early cortical components are a result of temporal lobe lesions do not necessarily reflect damage to the primary auditory cortex per se but rather the degree of damage to adjacent areas. They suggest that the effect of cortical lesions on Pa symetry may be due to retrograde degeneration of the thalamus extensive enough to involve thalamic nuclei other than the ventral nucleus of the medial geniculate body. Candidate generators include the medial and dorsal groups of the medial geniculate body with widespread projections that include the superior temporal plane, as well as the parietal opercula and inferior parietal lobes.

3.4. *The brainstem response*

Sohmer and Feinmesser succeeded in recording the eighth nerve action potential in 1967. As its magnitude was less than one microvolt, this would have been impossible without the improvement

in amplifiers which had taken place in the 50's and 60's. The technique aroused little interest until 1970 when Jewett confirmed its validity.

Since their discovery there has been much discussion about the anatomical origin of the brainstem waves. Jewett (1970) postulated, on the basis of recordings in the cat, that there were 4 vertex positive waves following the action potential which he related to specific generators within the brainstem. The brainstem auditory evoked response became a potentially clinically valuable tool. From recordings in man in 1971, Jewett and Williston showed that these acoustically generated 'early' potentials could be detected over a wide area of the skull.

A number of workers have correlated neuropathological lesions with abnormalities in the brainstem waveform (Lev and Sohmer 1972; Sohmer, Feinmesser and Szabo 1974; Starr and Achor 1975; Stockard and Rossiter 1977; Maurer et al. 1980). The conclusions were that the first wave arose from the cochlear nerve, the second from the cochlear nucleus, the third from the superior olivary complex and the fourth and fifth waves from the inferior colliculus. Abnormalities of wave I and all subsequent waves were reported as a result of ipsilateral monaural stimulation of patients with cochlear and eighth nerve damage. This is consistent with a peripheral origin of the first wave. Abnormalities in wave II and all subsequent waves were reported in patients with pontocerebellar angle or lateral pontomedullary junction (cochlear nucleus) lesions. Abnormalities in wave V were associated with midbrain lesions. However, midbrain lesions above the inferior colliculus resulted in a normal wave V.

Stockard and Rossiter (1977) and Maurer et al. (1980) further demonstrated abnormalities beginning at wave III with caudal pontine lesions and abnormalities of wave VI with rostral midbrain and caudal thalamic lesions. This is consistent with the generation of wave VI at the level of the medial geniculate body. Buchwald and Huang, in 1975, confirmed these origins by experimentally produced lesions in cats. However their suggestion of a pontine nuclear origin (nucleus of the lateral lemniscus) of wave IV conflicts with that of Lev and Sohmer (1972) and Jewett

(1970) who suggest that this wave originates from the midbrain along with wave V. The neuropathologic data in man (Stockard and Rossiter 1977) are consistent with either a rostral pontine or caudal midbrain origin for wave IV but favour a locus distinct from that of wave V on account of the abnormal degree of separation seen in these components in multibrainstem demyelination. Fig. 3.1. shows the origins of the brainstem components as proposed by Maurer et al (1980). However, Møller et al. (1981) have proposed that the second wave originates from the intracranial portion of the cochlear nerve, the third from the cochlear nucleus and the fourth and fifth from more peripheral nuclei of the ascending pathway than the earlier workers suggested. Wada and Starr (1983) provided evidence from experiments in cats that wave V is generated from the the region of the inferior nucleus of the lateral lemniscus. They found wave III to be dependent upon activity from the contralateral superior olivary complex.

It is unlikely that individual waves receive contributions from only one anatomical site. Stockard, Stockard and Sharbrough (1980) summarised the conflicting opinions with the statement that waves I, III and V primarily represent volume-conducted electrical activity from the acoustic nerve, pons and midbrain respectively, and that the latencies between these three potentials indirectly reflect neural conduction in the corresponding segments of the central auditory pathway.

CHAPTER 4

FACTORS AFFECTING THE AUDITORY EVOKED RESPONSE

4.1. *Introduction*

In recording the auditory evoked response a number of factors need to be considered as these may affect the waveform, and hence any measurement derived from it. The context in which the technique is to be applied is clearly important. Most of the work on the AER has been carried out to assess hearing thresholds, neurological or cognitive functions and has usually been done in 'awake' subjects. The requirements for the application central to this thesis, that is, to measure 'depth of anaesthesia' may produce different criteria.

The factors affecting the response have been divided into:-

4.2. Technical

4.3. Subject related

4.4. Pharmacological

Their effects on the brainstem, early and late cortical sections of the response in man are briefly reviewed.

4.2. *Technical factors*

4.2.1. *Recording system*

Electrode placements: The early and late cortical responses, which are 'near-field' responses, that is the generators are near to electrode sites, are more dependent on electrode position than the 'far-field' brainstem responses (Picton et al. 1974). However, clear components of the brainstem, early and late cortical responses can be obtained from a pair of electrodes, one on the vertex and one on the mastoid. A chin, forehead or opposite mastoid electrode is usually used as the earth. For early cortical recordings the inion site may be preferred to the mastoid so as to reduce the likelihood of contamination from the post auricular muscle potentials. This evoked muscle response occurs between 12

and 20 ms and can completely obscure the early cortical waves Pa and Nb. A mastoid electrode however gives somewhat better definition of the brainstem waves. In the investigations in this thesis the inion site was used for early cortical response measurements and the mastoid site for brainstem response measurements.

Amplifiers: For use in the operating theatre the amplifiers must provide good rejection of any electrical noise occurring at both inputs (common mode rejection). They should be well isolated at diathermy frequencies to prevent damage to the amplifiers themselves, and to protect the patient from diathermy burns. Additionally amplifiers with a low intrinsic noise level are required.

Filtering: Filter settings have to take into account the frequency composition of the section of the response of interest. A compromise has to be reached between a) rejecting unwanted frequencies from the EEG and other sources so reducing the variability of the response and b) accepting the signal of interest. Filtering around the critical frequency of the response may severely attenuate the response. Digital filtering is preferable to analogue filtering as the latter can produce changes in latency and can distort the signal excessively. It should be borne in mind that the frequency content of both signal and noise may be changed by the treatments or effects which are being studied e.g. age, sleep, anaesthetic drugs. The range of filter settings in common use are:-

Section of response	Filters (Hz)	
	high pass	low pass
Brainstem	100-500	1600-3600
Early cortical	1-30	100-500
Late cortical	0.01-1.5	15-100

Boston and Ainslie (1980) assess the effects of different types of filtering on the brainstem response. They claim that low pass filters settings above 1600 Hz should not alter the response substantially.

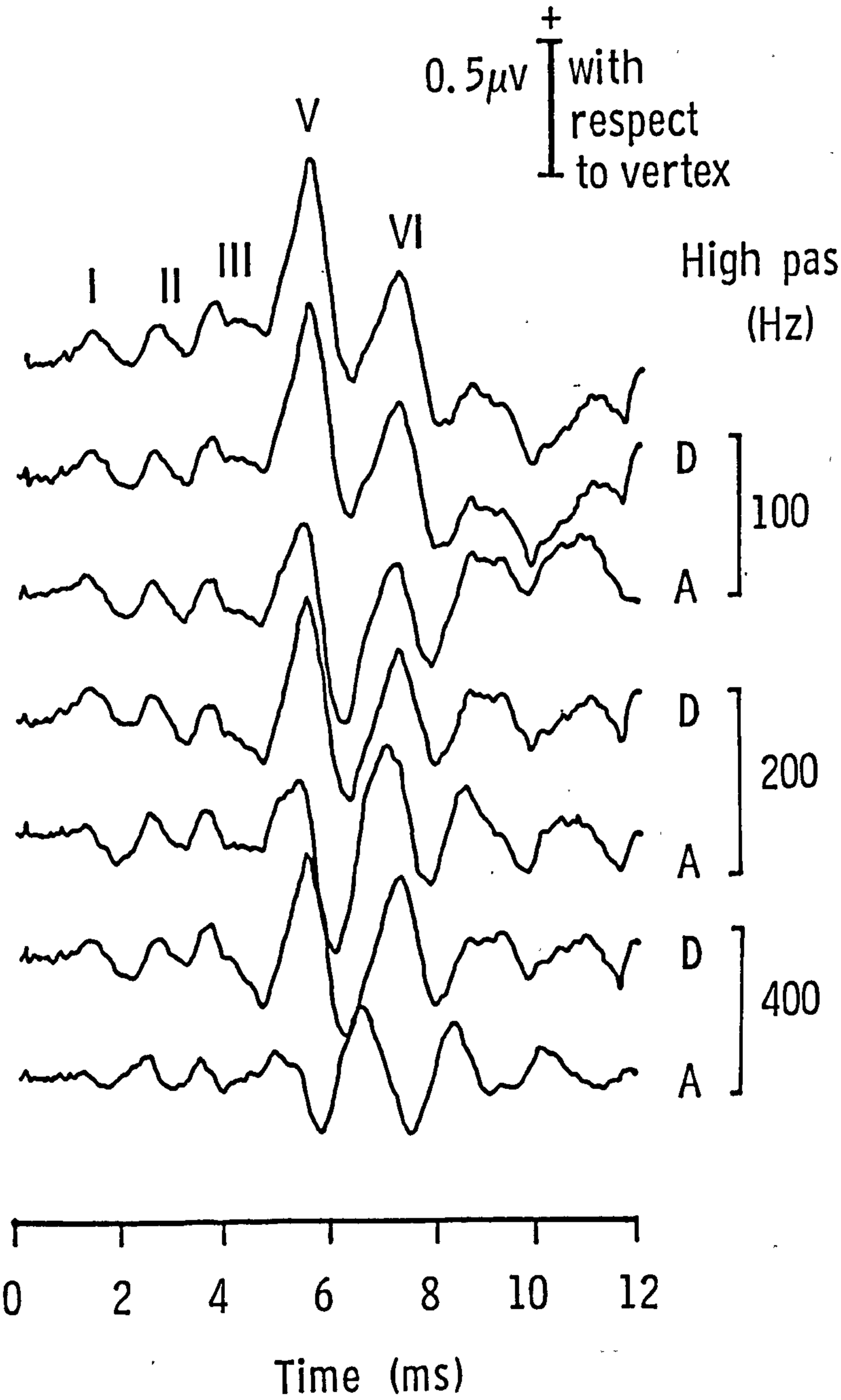


Fig.4.1. Effects of analog (A) and digital (D) high pass filtering on the brainstem response. (Electrodes:- vertex to ipsilateral mastoid; stimulus 70 dB clicks; low pass filter set at 3000 Hz.) (After Boston and Ainslie, 1980).

The range of high pass filter settings used, by different investigators, to filter the brainstem response is more of a problem. The data of Boston and Ainslie, showing the effect of high pass digital and analog filtering, are reproduced in Fig.4.1. With an increase in high pass filtering from 100 to 400 Hz the analog filter produced several significant changes in the response. The early waves became less well defined. Wave V decreased while wave VI increased probably due to the loss of slow wave activity on which the unfiltered response is superimposed. The latencies increased by up to 0.5 ms. In the digitally filtered response, the amplitude of wave III was increased slightly and the amplitude of wave V decreased slightly. The latencies of the waves were unaltered. Doyle and Hyde (1981) confirmed these findings.

The early cortical response can be altered fundamentally by low pass filtering. The low pass filter settings of 100 Hz used by some workers (Goldstein and Rodman 1967) can result in a brainstem response which is so smoothed that the individual waves are unrecognisable. Such workers have labelled this highly filtered brainstem response Po whereas others have labelled the vestigeal post auricular muscle response Po (Kavanagh et al. 1984). This difference in nomenclature has been discussed at length in section *3.3.1.* Changing the low pass filter to a lower frequency setting can, however, be very helpful for removing muscle artefact.

The high pass filter settings used to derive the early cortical response can affect the variability of the response considerably. For instance, Ozdamar and Kraus (1983) using a high pass filter set at 3 Hz (low pass at 2000 Hz) describe 3 types of early cortical response waveforms found in the same subjects within a recording session (Fig.4.2.). These are:-

a) a double peaked waveform - Pa and Pb seperate

b) a broad Pa

c) an absent Pb distinct Pa only.

One possible explanation for the variability in the waveform with time is contamination with low frequency EEG due to insufficient high pass filtering. Suzuki et al. (1983) showed that the main frequency constituents of the early cortical response in adults range between 30 and 50 Hz. Their data (Suzuki et al. 1984),

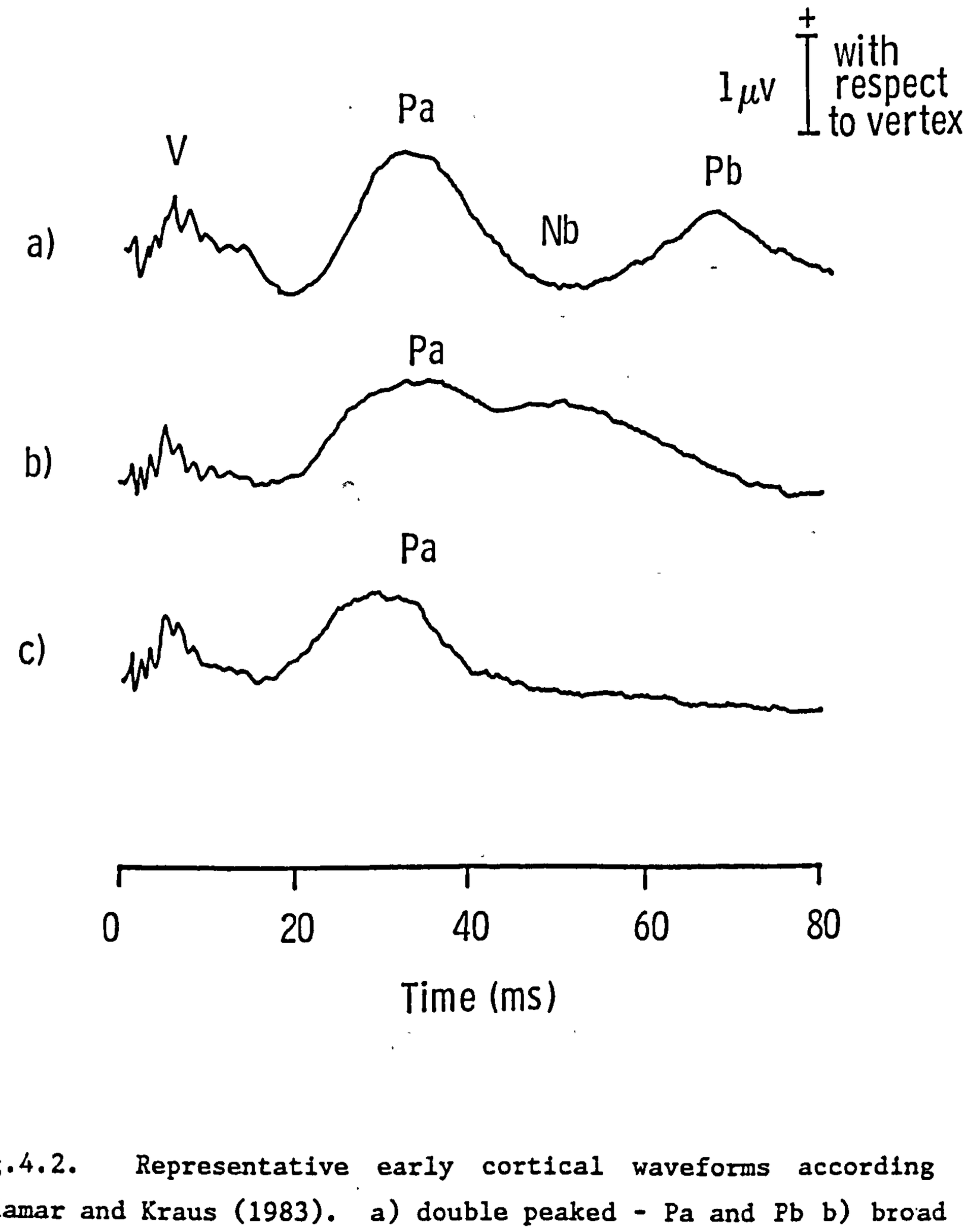


Fig.4.2. Representative early cortical waveforms according to Ozdamar and Kraus (1983). a) double peaked - Pa and Pb b) broad Pa c) absent Pb, distinct Pa only.

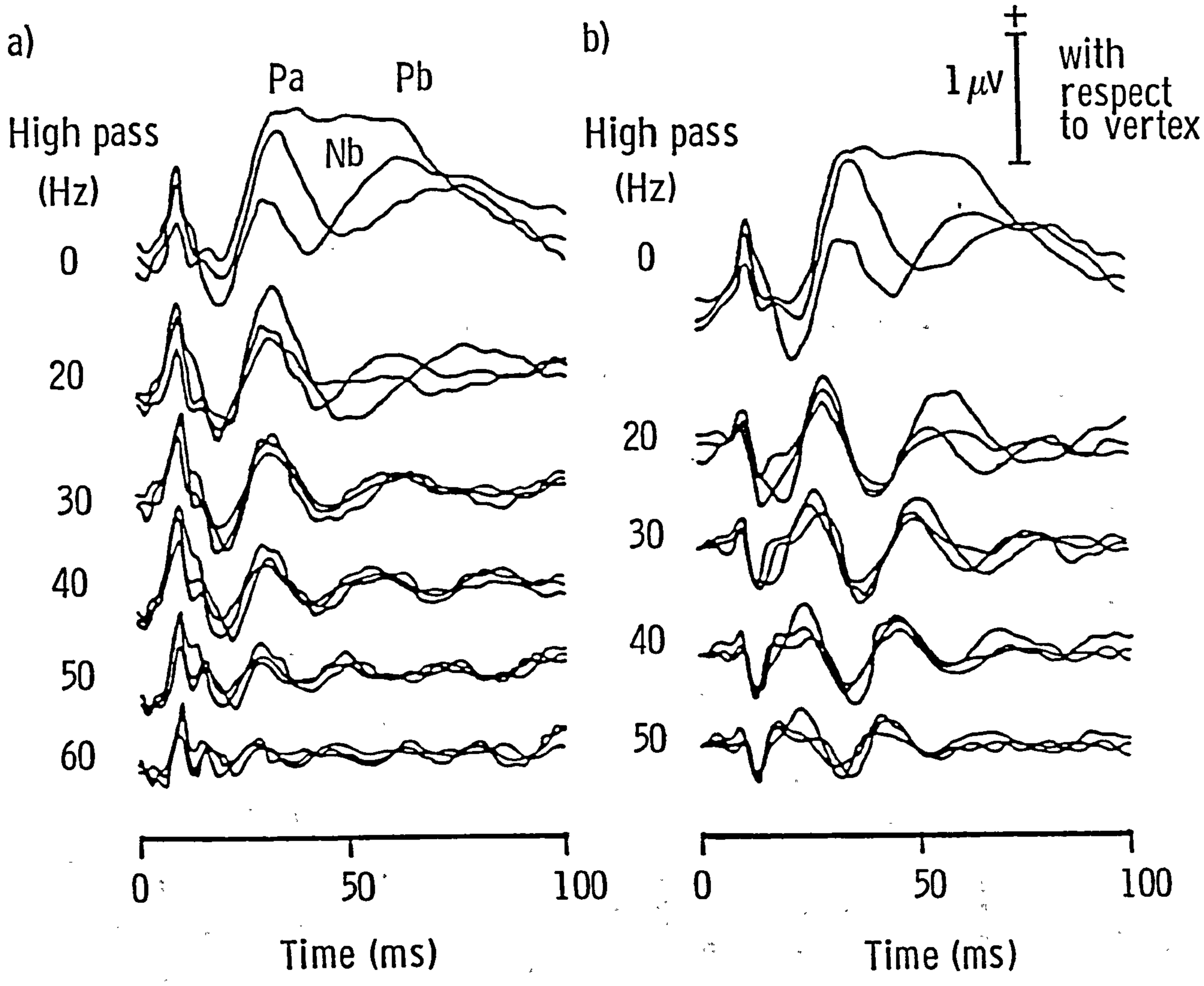


Fig.4.3. Early cortical responses in 3 subjects (taken from Suzuki et al. 1984). Effects of a) digital b) analog high pass filtering. Low pass filter set at 200 Hz.

which demonstrate the effect of high-pass filtering on the early cortical responses of 3 subjects are shown in Fig.4.3. At the 0 Hz high pass filter setting there is considerable variability between the subjects. As the high pass filter setting is increased to 40 Hz the subjects' responses become closely coincident. Further at 0 Hz the response of one of the subjects is the b) type described by Ozdamar and Kraus whereas at 30Hz it is the a) type, consisting of a seperate Pa and Pb. Compared to the digital filtered responses (Fig.4.3.), the analog filtered responses are characterized by enhancement of the later components (Nb and Pb), and latency decrements of Pa, Nb and Pb.

Scherg (1982) is in agreement with the above workers concerning the marked effects of high pass filter settings on the early cortical waveform but makes further recommendations as to the appropriate filters to use. Filters are commonly defined in terms of a) the cut-off frequency, that is, the frequency at which the signal becomes significantly attenuated and b) the filter slope, that is, the rate of attenuation of the signal as a function of frequency. Filters are also characterised by the phase shift or delay they produce at different frequencies. Scherg believes that digital zero-phase shift filters should be used wherever possible to avoid distortion of the waveform by delaying components of different frequencies by different amounts. If analog high pass filters are unavoidable the filter slope should be shallow (preferably 6 dB/oct) and cut off frequency below 10 Hz. He demonstrated that analog filters with steep slopes can distort the waveform producing artificial components due to damped oscillations after the time event. However, this cannot apply to the data of Suzuki et al. (1984) shown in Fig.4.3. because the same number of components are seen in the digital and analog filtered traces at comparable high pass filter settings even though analog filtering at 24 dB/octave appeared to enhance the later components.

It has been suggested that the interpretation of physiological function (Scherg 1982) and generator sources (Musiek et al. 1984) should be based on wide-band recorded signals the implication being that such signals most closely represent the underlying physiological processes. However, it should be borne in mind that it is not possible to record a 'true' biological signal, in that,

when an electro-potential is recorded from the surface of the scalp, it has already been processed (volume conducted through the brain tissue and diffused by the scalp). More important is that the processing should be relevant to the situation under study. In some situations, consistency of the morphology of the response between individuals and between trials (robustness) is of paramount importance, whereas, in others it is the differences in the response between individuals and groups (sensitivity) that matter. For example, if the change in the response is to be used to measure depth of anaesthesia, differences in the response due to the age of the individuals, which are not related to anaesthetic depth, are unwanted. On the other hand, if a study is specifically concerned with the effects of ageing on the response, care should be taken not to remove such effects by too much filtering. In addition, average responses over short time periods may be required to monitor the changing brain state of the patient due to sleep or drugs. (Signal averaging assumes that the response is stable over the period during which it is sampled and yet in situations where the brain state is changing this is unlikely and hence the average could be meaningless.) McFarland et al. (1975) by experimentation with filter settings found that with a filter band pass of 25-175 Hz they could obtain identifiable and repeatable responses with as few as 128 stimuli. Most important is to understand the effect that signal processing is likely to have on the averaged waveform.

4.2.2. *Stimulus*

Types of stimuli: Either clicks or tone bursts may be used to evoke the response. The brainstem and early cortical responses, which have relatively short onset latencies, are best evoked by clicks with a fast rise time and short duration such as is produced by a 100 to 500 μs electronic square wave (Beiter and Hogan 1973; Skinner and Antinoro 1971; Scherg and Volk 1983). However, such a click stimulates the whole basal portion of the cochlea almost instantaneously and thus does not produce frequency specific information about hearing defects. Audiologists have therefore attempted to produce these responses with some frequency specificity i.e. filtered clicks (Zerlin et al. 1973; Coats et al. 1979) and tone pips (Scherg and Volk 1983; Davis and Hirsh 1979; Maurizi et al. 1984; Kileny 1986; Vivion et al. 1980).

The late cortical waves, on the other hand, can be produced by tone bursts of several millisecond duration which allows for excellent frequency specificity. A rise time of 25-30ms with a duration of 25-50 ms has been recommended for this purpose (Skinner and Jones 1968; Onishi and Davis 1968). Psychologists wishing to use the late cortical responses to assess cognitive processes (Donchin et al. 1978) can use combinations (paradigms) of stimuli for example, short and long duration or frequent and infrequent stimuli.

Initial phase of the stimulus: The polarity of the click has been shown to affect the brainstem latencies and the conflicting opinions are discussed by Salt and Thornton (1984). Rarefaction clicks are produced by initial movement of the headphone transducer away from the tympanic membrane and condensation clicks by initial movement towards it. Click phase is unlikely to have any effect on the early or late cortical waves.

Binaural stimulation: When the stimulus is applied binaurally all sections of the response increase in amplitude (Davis and Zerlin 1966; Blegvad 1975; Robinson and Rudge 1981; Woods and Clayworth 1985). For example, a 50dB stimulus presented binaurally will give brainstem waves of the same amplitude as an 80dB stimulus presented monaurally (Blegvad 1975). Recording from electrodes contra-lateral to the stimulated ear as opposed to ipsilateral may also make a difference to the waveform. Since wave I is of peripheral origin it is not seen in contralateral brainstem recordings (Terkildsen et al. 1973). Of the early cortical waves Na is larger in amplitude and shorter in latency contralateral to the stimulated ear whereas with Pa and Nb there are no differences due to ipsi- and contra-lateral stimulation (Woods and Clayworth 1985). Asymmetries have been noted in some components of the late cortical response (McCallum and Curry 1979; Perrault and Picton 1984).

Stimulus intensity: Increasing the intensity from threshold to around 70dB HL (above this muscle artefact can be a problem) increases the amplitude and decreases the latency of all sections of the response (Davis and Zerlin 1966; Madell and Goldstein 1972; Tepas et al. 1972; Terkildsen et al. 1973; Picton et al. 1974 ;

Thornton et al 1977; Ozdamar and Kraus 1983; Scherg and Volk 1983; Maurizi et al. 1984; Bruneau et al. 1985). There may be further changes above this stimulus level in some components of the evoked response.

Stimulus presentation rate: Increasing the stimulus presentation rate can reduce the time taken to carry out the test which is an important clinical consideration. The number of stimuli needed to produce a clear averaged response depends on the amplitude of the response in relation to the background noise. However, increasing the stimulus presentation rate above a certain value has been shown to reduce response amplitude due to stimuli being presented within the refractory period of the previous response and due to responses overlapping. When responses overlap, where deflections of opposite polarity add together amplitudes are reduced. The 40Hz 'steady state' evoked response described by Galambos et al. (1981) is a special case of overlapping responses. The stimulus is presented at 40 per second (one every 25ms) and since the 3 major peaks of the early cortical response occur at 25 ms intervals, the overlapping effect in time of these waves enhances their amplitude. Under normal circumstances a compromise has to be reached between the clarity of the response and the time taken to obtain it.

Increased latencies and reduced amplitudes of the brainstem waves with increasing stimulus presentation rates up to 80 per second have been demonstrated (Picton et al. 1974; Terkildsen et al. 1975; Hyde et al. 1976; Robinson and Rudge 1977; Campbell and Bartoli 1986). The early brainstem waves start to diminish with stimulus presentation rates in excess of 10 per second although wave V amplitude is relatively well preserved even at the very high rates and can be used to determine auditory thresholds at rates up to 50 per second. At rates in excess of this, myogenic responses such as the post auricular response, become superimposed on the recording making interpretation difficult. Generally, presentation rates between 10-20 per second are used so that 1000-2000 stimuli can be presented in 1-2 minutes.

There has been very little in the way of formal study on the effect of stimulus presentation rate on the early cortical response. When Geisler and his co-workers first described the response in 1958 they commented that high stimulus presentation rates may serve to decrease the amplitude of the early cortical waves. Picton and co-workers (1974) demonstrated a marked reduction in the amplitude of the early cortical waves when stimulus presentation rates were increased from 4 to 16 per second. Goldstein et al. (1972) and McFarland et al. (1975) found little change in Pa across the rates of 1 to 15 per second. Erwin and Buchwald (1986a) found that the Pa-Nb amplitude measurement was not affected up to rates of 10 per second although Pa latency was increased. Most workers use the stimulus presentation rate of 6-10 per second so that 512 stimuli can be presented in 1-2 minutes.

The late cortical components are reduced in amplitude and their latencies increase with increased stimulus presentation rate. However, substantial changes occur at much slower rates than with the brainstem and early cortical components. Erwin and Buchwald (1986a) found that the Nb-P1 amplitude measurement became significantly reduced between stimulus presentation rates of 1 to 5 per second. Picton and co-workers (1974) demonstrated a substantial reduction (greater that 50%) between 0.25 and 1 per second in the P1-N1-P2 complex. Davis and co-workers (1966) reported that the late cortical response took approximately 10 seconds to recover after each stimulus before it could be fully evoked again suggesting a stimulus presentation rate of 0.1 per second. Such slow stimulus presentation rates would clearly be unrealistic. Most workers average 64 responses and use stimulus presentation rates of 0.5 to 1 per second which allow an average to be obtained in 1 to 2 minutes.

Irregular stimulus presentation rates: Tyberghein and Forrez (1969) found a stimulus applied in a random rather than a regular sequence produced larger late cortical waves. This may be due to the attention of the subject being increased. Randomization of the stimulus also aids the averager in suppressing any regular source of interference such as EEG and 50 Hz interference.

4.3. *Subject related factors*

4.3.1. *Temperature*

Hypothermia progressively increases brainstem (Stockard et al. 1978; Markand et al. 1987) and early cortical latencies (Kileny et al. 1983) and reduces their amplitudes until at around 20 °C they virtually disappear. Hyperthermia shortens brainstem latencies (Bridger and Graham 1985). There is no information on the effect of temperature on the late cortical response.

4.3.2. *Age and Gender*

There is a great deal of discussion among clinicians as to how age and gender affect the various sections of the response and whether separate standards need to be established for males and females and for different age groups.

The weight of evidence is that from neonates to 2-3 year old infants the latencies of the brainstem waves decrease (Hecox and Galambos 1974; Salamy et al. 1976; Starr et al. 1977). From adolescence to old age the latencies increase and are longer in males than females (Beagley and Sheldrake 1978; Rosenhall et al. 1985; Chu 1985; Thivierge and Côté 1987) and this is not solely due to differences in head size (Trune et al.1988). Amplitudes decrease with age (Beagley and Sheldrake 1978; Psatta and Matei 1988) and are higher in females than in males (Chu 1985).

The early and late cortical responses have been much less studied in these respects. Whether the early cortical response differs between adults and children is a controversial issue. The argument revolves around the identifiability of the response, which is poor, in infants and children (Kraus et al. 1987). In addition, the early cortical waves have been reported to be dramatically reduced in amplitude (Collet et al. 1988a) or absent (Okitsu 1984) in infants and young children during sleep. However, many previous reports as well as current studies have demonstrated robust stable early cortical responses from infants and children (McRandle et al. 1974; Wolf and Goldstein 1978; Mendelson and Salamy). Interestingly, practically all reports of good stable early cortical responses in children use high pass filters above 20-25 Hz. Suzuki et al. (1984) studied the

variability of the early cortical response waveform in children and concluded that high pass filters of less than 20 Hz are insufficient to eliminate the low frequency brain activities which contaminate the response. However they warn that as the dominant frequency of the early cortical components of the response in children is around 25 Hz as compared to 40Hz in adults, 20 to 25Hz high pass filters would produce more serious waveform alterations in children than in adults. Collet et al. (1988a) had used a high pass filter of 2 Hz to record the response in infants, in which case the response was probably inseparable from the background EEG. Okitsu's (1984) recording appeared to be adjusted to accommodate a large post-auricular muscle response of which he seemed largely unaware. When this disappeared, understandably the early cortical waves were barely visible.

Even among workers who have successfully recorded early cortical responses in children, whether there are differences in the waveform between children and adults is still not resolved. Mendel et al. (1977) reported that the latencies for infants at 1 - 8 months of age were 2 to 5 ms shorter than those of adults for each peak, with a filter setting of 25 - 175 Hz (24 dB octave). Mendelson and Salamy (1981) found no trend for decreasing latencies as a function of age in the early cortical response recorded with analog filtering at 20 to 175 Hz (24 db octave). Suzuki et al. (1984) disagree with both groups. Suzuki et al. found that the latencies of Pa and Nb were still significantly longer than those of adults with both digital and analog filtering at 20 to 200 Hz.

Kelly-Ballweber and Dobie (1984) and Woods and Clayworth (1986) report increases in the amplitudes as well as the latencies of the early cortical waves in elderly compared to young people. The late cortical components, show increased latencies (P2 and P3) and reduced amplitudes (P3) with age (Goodin et al. 1978; Pfefferbaum et al. 1979; Picton et al 1984; Hergerl et al 1985). The reports on the effects of gender on the cortical responses show females having higher amplitudes than males (Woods and Clayworth 1986; Picton et al. 1984; Hergerl et al. 1985).

4.3.3. *Level of arousal*

The brainstem response is remarkably stable during sleep (Picton et al. 1974; Erwin and Buchwald 1986b; Campbell and Bartoli 1986; Bastuji et al. 1988).

Sleep is reported to have little (Mendel and Goldstein 1971) effect on the early cortical response and as a consequence the blood level of sedative drugs given during recording sessions are never measured and the stage of sleep is rarely mentioned. While it is true to say that Pa latency is hardly affected by sleep the subject merits further discussion because sleep produces a fundamental change in the early cortical waveform.

Natural sleep has been divided into five stages (see Fig.3.6.) by Rechtschaffen and Kales (1968) depending on eye movements and EEG changes. Stage 1, which is the period of drowsiness just prior to sleep is associated with a lowering of the frequency of the EEG and a reduction in the amount of alpha rhythm. The start of stage 2 is 'sleep onset'. In this stage, sleep spindles (bursts of fast EEG activity) and K complexes (high voltage, slow frequency waves) occur. Stage 2 can develop into stages 3 and 4, referred to as 'slow wave' sleep because more and more high voltage slow waves occur. Alternatively it may proceed to REM, which is characterised by mixed frequency low voltage EEG activity and rapid movements of the eyes. Slow wave sleep is generally referred to as 'deep sleep' whereas REM sleep is associated with a type of mentation referred to as 'dreaming'.

Erwin and Buchwald (1986b) studied the effect of stage of sleep on the early cortical response recorded with a time base (0-100ms) and fliter settings (10-300 Hz) which allowed wave V, Pa and Pb to be recorded simultaneously. Their data are shown in Fig. 4.5. With a change in sleep stage from awake through stage 2 to stages 3 and 4 the early cortical response waveform loses the central peak Pb. Pa is relatively stable Nb latency increases and Pb returns during REM sleep. The data of Osterhammel et al. (1985) showed similar changes although they did not distinguish between stage 1 and REM.

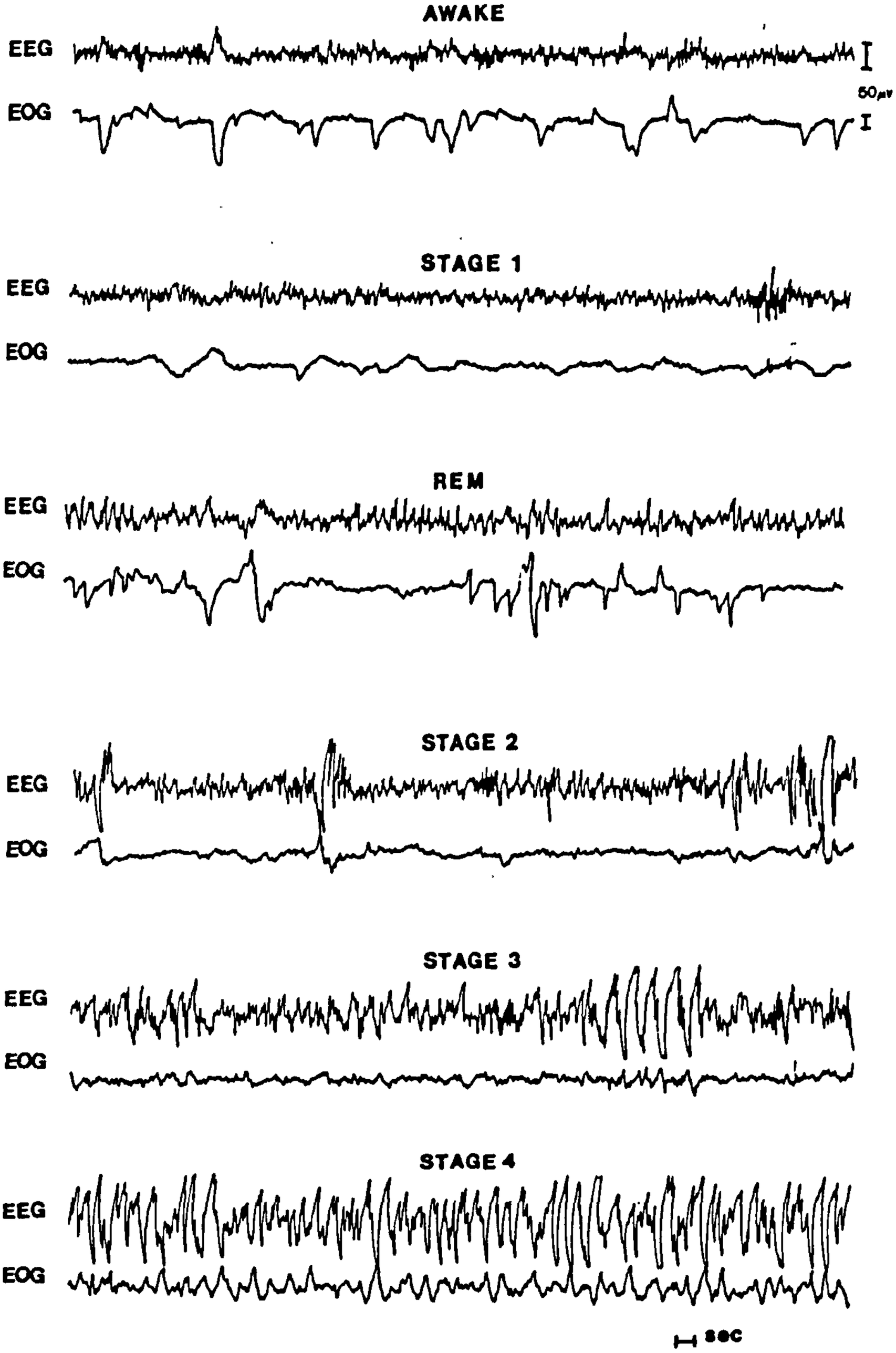


Fig.4.4. Examples of EEG and eye movements (EOG) recorded during wakefulness, sleep stages 1, REM, 2, 3, and 4. Classification according to Rechtshaffen and Kales (1968).

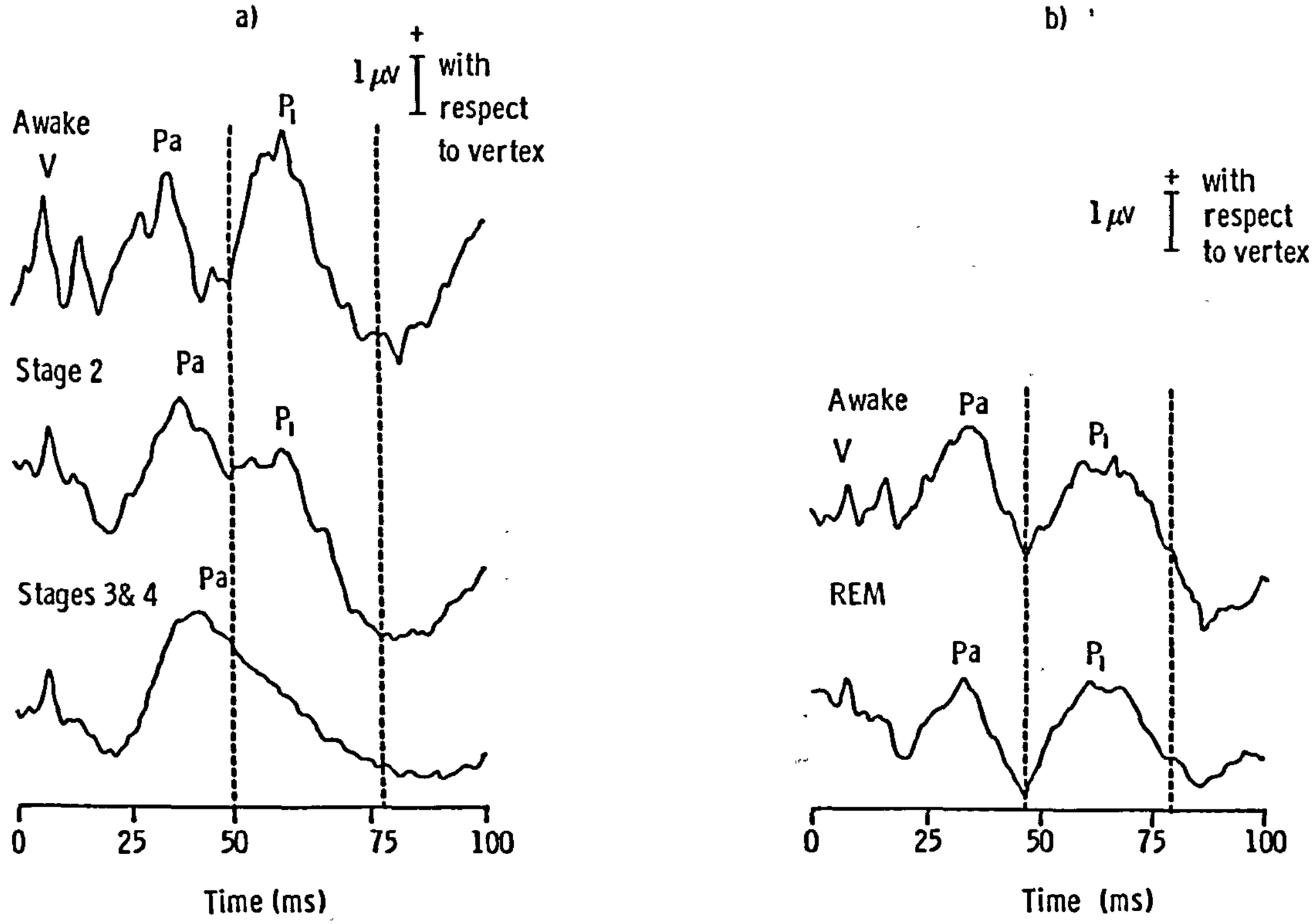


Fig.4.5. Changes in the early cortical response a) from wakefulness through stage 2 to stages 3 and 4, and b) from wakefulness to stage REM (after Erwin and Buchwald 1986b). Pb (labelled P1) is present during the awake state but gradually disappears as the subject progresses through stages 2, 3 and 4. The amplitude and latency of Pb during REM sleep are similar to those in the awake state.

In a series of careful studies the above workers (Buchwald et al 1981; Hinman and Buchwald 1983; Chen and Buchwald 1986; Erwin and Buchwald 1986a; Erwin and Buchwald 1987) explored the generators of this sleep sensitive sytem. They validated the cat early cortical response as a model appropriate to man (see also section *3.3.3.*). On the basis of comparable effects of stimulus rate, sleep and binaural interaction properties (wave A and Pb do not show binaural occlusion) they concluded that the waves 7 and A in the cat are homologues of Pa and Pb in man. They therefore suggested from the origins of wave A in the cat (Hinman and Buchwald 1983) that Pb in man reflects a generator system which projects from the cuneiform nucleus, through the medial tegmentum to the medial thalamus. They speculate that this generator system could mediate physiological correlates of 'state' modulate sensory input or motor output or it could provide integrative mechanisms for the focusing of auditory attention.

Their work makes another important contribution to understanding the early cortical response. It gives second possible explanation as to the 3 representative types of early cortical waveforms described by Ozdamar and Kraus in 1983 labelled a), b) and c) of Fig.4.2. section *4.2.1.* The early cortical response during the awake state and REM sleep described by Erwin and Buchwald (1986b) and shown in (Fig. 4.5.) is the same as a) i.e. the doubled peaked - Pa and Pb. The response during stage 2 sleep is the same as b) i.e. a broad peaked Pa. The response during stage 3 and 4 sleep is the same as c) i.e. a distinct Pa. In other words the data of Ozdamar and Kraus may be showing the transition from awake (or REM) to stage 4 sleep. It is quite possible that b) is a result of averaging responses of types a) and c) and in itself is meaningless.

These observations are particularly relevant to the recording of the early cortical response in infants and young children who are frequently given sedatives to make them relax or sleep during the investigation. Their waveforms could be any combination of the three 'representative' responses. If, in addition the high pass filter settings were too low to ensure adequate rejection of the background EEG frequencies, the low detectibility of the early cortical waves in infants and young children is not surprising.

Sleep has a dramatic effect on the late cortical waveform (Picton et al. 1974). The changes in Pb/P1 have already been discussed. Another very striking change is the considerable enhancement of the N2 component. This may be equivalent to the K-complex seen in the unaveraged sleep EEG. This increase in N2 is generally associated with increased latency and decreased amplitude of the N1-P2 components. The waveform is so altered that peak identification is in question.

The brainstem response is unaltered by changes in the level of alertness or attention (Picton and Hillyard 1974; Davis and Beagley 1985; Collet et al. 1988b). Whether the early cortical response is affected by selective attention remains controversial, some workers reporting increased amplitudes (Woldorff et al. 1987) others being unable to demonstrate significant changes (Picton and Hillyard 1974; Collet et al. 1988b). Increased amplitudes of the late cortical responses have been shown to be associated with higher levels of vigilance (Romani et al. 1988) and alertness or attention (Hillyard et al. 1973; Picton and Hillyard 1974).

4.3.4. *Neurological factors*

Disorders such as multiple sclerosis (Robinson and Rudge 1977) or tumours which affect the auditory nerve tract (Sohmer et al. 1974; Starr and Achor 1975; Maurer et al. 1980; Robinson and Rudge 1983; Woods et al. 1987) have an effect on the response. Information on such lesions has been used to confirm the generators of the various waves (see **Chapter 3**). Clearly, impairment of the peripheral auditory structures would also diminish the response as would factors which affect the brain, such as coma (Starr and Achor 1975) and narcosis.

4.4. *Pharmacological factors*

4.4.1. *General anaesthetic agents*

The early anaesthetics: Ether, vinyl ether, chloroform, ethylene, trichloroethylene and, cyclopropane had almost disappeared from anaesthetic practice by the time computer averaging of the evoked responses was introduced and therefore their effects on the auditory evoked response have not been studied . However, nitrous oxide is still widely used as a background gas. It has been

investigated at subanaesthetic concentrations by a number of workers. Sebel, Flynn and Ingram (1984) found no effect of 50% nitrous oxide in oxygen on the brainstem response. Lader and Norris (1968) studied the effect of 25% nitrous oxide on the response from 20-250ms (although it is not clear precisely to which waves they are referring). They found the early cortical waves and the latencies of the late cortical waves not significantly affected but the amplitudes of what were probably P1, N1 and P2 were significantly reduced. Harkins, Bendetti, Golpitts and Chapman (1982) also found that the amplitudes of the late cortical peaks N1 and P2 amplitudes were reduced by 50% nitrous oxide and Houston, McClelland and Fenwick (1988) demonstrated a linear decrease in the amplitude of these waves with 0 to 40% nitrous oxide. In both of these studies nitrous oxide did not appear to affect the latencies.

The fluorinated hydrocarbons: The literature on these is discussed in more detail in **Chapter 11**, alongside the findings of the thesis. At the time of registration (September 1983) halothane had been reported to have no effect on the brainstem response by Duncan, Sanders and McCullogh (1979). In 1981, 1982 the Clinical Research Centre (CRC) group had reported that increasing concentrations of both enflurane (Thornton et al. 1981, 1982) and halothane (Thornton et al. 1982) increased brainstem waves latencies III and V and interpeak intervals I-III, I-V and III-V. In 1982 Dubois and co-workers (1982a, 1982b) confirmed the enflurane findings.

At the time of registration of the thesis the effect of the modern inhalation agents on the early or late cortical peaks had not been studied except by the CRC group (Thornton et al. 1981, 1982) and by Celesia and Puletti in 1971, who recorded from electrodes placed directly on the cortex. They found that halothane increased the latency and reduced the amplitude of waves, which they labelled P1, N1 and P2, which may correspond to the Po, Na, Pa waves obtained from scalp recordings. The CRC group found increased latencies and reduced amplitudes of waves Pa and Nb with increasing concentrations of halothane and enflurane. These changes were similar in appearance over the clinical concentration range. There were no studies reported in the literature on the effects of these anaesthetic agents on the late

cortical waves nor of the other fluorinated derivatives (methoxyfluorane, fluroxene etc.) on either early or late cortical waves.

The intravenous anaesthetics: With the exception of the barbiturates there have been few studies on the effect of the intravenous general anaesthetics on the auditory evoked response. Duncan, Sanders and McCulloch (1979) found no effect of thiopentone on the brainstem response. However, methohexitone for electro-convulsive therapy, was shown by Kriss, Prasher and Pratt (1982) to increase the latencies of waves III and V. Goff, Allison and Lyons (1977) and Hall (1985) have demonstrated alterations in the early cortical response with high doses of barbiturates. Mendel and Hosick (1975) studied the effect of sedative doses of secobarbital and found small increases in latency of the early cortical waves Pa and Nb in contrast to a marked depression of the late cortical waves N1, P2, N2 (Hosick and Mendel 1975).

Bertoldi and co-workers (1983) were unable to demonstrate an effect of etomidate on the brainstem response and found the effect of ketamine to be equivocal.

4.4.2. *Opiates - analgesics*

The effect of fentanyl on the brainstem response has been studied by Velasco et al. (1983), Samra et al. (1984) and Loughnan et al. (1987) and of morphine by Samra and Morris (1986). No group found any effect on brainstem latencies. There are no reports in the literature of the effects of opioids on the early cortical responses. Opioids and opioid antagonists modify the increase in amplitudes of the late cortical waves with selective attention. Opioids diminish this effect and opioid antagonists such as naloxone augment it (Velasco et al. 1983; Arnsten et al. 1984).

4.4.3. *Sedatives*

Where they have been studied, drugs such as the benzodiazepines have little effect on the brainstem and early cortical responses (Ozdamar & Kraus 1983; Adams et al. 1985; Loughnan et al.1987). Acute alcohol intoxication has been reported to produce increased brainstem wave latencies, not due to the depression of core temperature which occurs at the same time (Squires et al. 1978;

Church & Williams 1982). Ethanol has been shown by Squires et al. (1978) to increase the latency of the early cortical wave Pa. Ethanol (Gross et al. 1966; Hari et al. 1979; Teo and Ferguson 1986; Campbell & Lowick 1987) and the benzodiazepines, diazepam (Herrmann et al.1981), triazolam (Johnson and Spinweber, 1981) and midazolam (Milligan et al. 1987), have been shown to increase the latencies and decrease the amplitudes of the late cortical waves. Haloperidol (Herrmann et al. 1981) and chlorpromazine (Laurian et al 1981) had little effect on these waves.

In conclusion, a perplexing number of factors modify the auditory evoked response with no consensus as to the precise way in which they do so. The above review is an over-simplification because it has not mentioned that these factors interact, e.g. stimulus repetition rate modifies the effect of stimulus intensity, filter effects can obscure age effects etc. The nature of their interactions result in even more disagreement. It does however emphasize the need to standardize variables which are not of direct interest, such as stimulus intensity and presentation rate, so that they do not interfere with the interpretation of the effects of the variables that are central to the study. It also highlights the need to carry out within subject comparisons to eliminate the variability due to factors such as age and gender.

From the above review the different sensitivities of the various sections of the auditory evoked response to different factors become apparent. For instance, the brainstem response is sensitive to pathological changes and stimulus parameters but not so much to drugs. The late cortical response on the other hand is very much affected by sleep, sedation and even by changes in the level of alertness. The early cortical response on account of its intermediate position therefore seemed the most likely area in which to find graded changes with 'depth of anaesthesia'.

SECTION B

METHODS

CHAPTER 5

STUDY DESIGN AND ANAESTHETIC PROTOCOL

5.1. *Introduction*

The experimental work presented in Section C of this thesis comprises nine studies involving 72 patients, who gave their informed consent to participate in the studies. Each study was approved by the Northwick Park Hospital Ethical Commitee. The aim of these studies, patient information, chapters in which the results are reported and precise sections in which the methods are described are given in Table 5.1.

Table 5.1. Summary of studies

Aim	No.	Sex	Age (yr)	Methods in:-
Chapter 8 - Effect of general anaesthetics on AER:-				
halothane	3	F,3M	18-45	5.2. & 5.3. 6.1. & 6.2. 7.1.- 7.4. & 7.5.1.
(+recovery)	2	M		
enflurane	2	F,4M		
isoflurane	5	F,1M		
etomidate	4	F,3M		
(+saline)	5	F,2M		
Althesin	6	F		
propofol	3	F,3M		
Chapter 9 - Effect of surgical stimulation on AER:-	11	F	18-50	5.2. & 5.4. 6.1.,2.,4. 7.1.- 7.4. & 7.5.2.
Chapter 10 - Correlation of AER with 'awareness':-				5.2. & 5.5. 6.1.1.,2.,4. 7.1.- 7.4. & 7.5.3.
before gen. surgery	1	F,6M	18-60	
during Caesarian sect.	8	F	18-40	

The standard anaesthetic protocol described in 5.2. was used wherever possible. Modifications and additional recordings which had to be made to suit the aims of a particular study are described in 5.3. to 5.5.

5.2. *Standard anaesthetic protocol*

Premedication	:-	10 mg morphine, 0.6 mg atropine - an hour before induction.
Induction of anaesthesia	:-	2-4 mg kg^{-1} sodium thiopentone
Relaxation	:-	0.1 mg kg^{-1} pancuronium
Tracheal intubation	:-	
Maintenance of anaesthesia	:-	70% nitrous oxide: 30% oxygen inspired conc.
Variables controlled	:-	$p'CO_2$ at 5kPa by adjusting ventilation
Variables measured	:-	Oesophageal temperature, tip of thermistor at level of aortic arch, measured continuously.
	:-	Arterial pressure and heart rate at 5-10 minute intervals.
	:-	EEG for subsequent AER analysis

5.3. *Effects of general anaesthetics on the AER*

In this series of studies the effects on the AER of increasing concentrations of six general agents were examined. These investigations took place before surgery started. The first concentration of test agent was added seven to ten minutes following the induction of anaesthesia, with the patient's lungs mechanically ventilated and anaesthesia maintained on nitrous oxide and oxygen as described in the standard protocol (see 5.2.). At 10 minute intervals the test concentration was raised either by

increasing the amount of agent added to the inspired gas or by increasing the infusion rate.

With the inhalation agents, inspired concentrations increased:-

halothane from 0.5 - 2.5% in 0.5% increments,
enflurane from 1.0 - 5.0% in 1.0% increments,
isoflurane from 0.75 - 3.75% in 0.75% increments.

With the intravenous agents, infusion rates increased:-

etomidate from 0.01-0.05 mg kg^{-1} min^{-1} in 0.01 mg kg^{-1} min^{-1} increments,
Althesin from 1.5-7.5 µl kg^{-1} min^{-1} in 1.5 µl kg^{-1} min^{-1} increments,
propofol from 40-200 µg kg^{-1} min-1 in 40 µg kg^{-1} min-1 increments.

The saline group in Table 5.1. refers to a group of six patients who were studied double blind and randomly interspersed in the etomidate study. In these patients an equivalent volume of saline was infused over the same time period.

Average AERs to the last 2048 stimuli (equivalent to 5.7 minutes) were obtained for the post-induction period and at each of the 5 concentrations. For the purpose of statistical analysis, the post-induction concentration was taken as zero. For the inhalation agents the concentration of the test period was taken as the mean end-tidal concentrations corresponding to the 5.7 minutes over which the AER was collected. For etomidate and Althesin, venous blood samples were drawn from the arm opposite to that receiving the infusion at the 5th and 10th minute of each test period and the mean serum etomidate or plasma alphaxalone concentration of these two samples was taken as the concentration during the test period. In the propofol study blood was similarly sampled at the 6th, 8th and 10th minute of the test period and the mean blood propofol of these three samples was taken as the concentration of the test period.

On a number of occasions there were delays between the end of the study and the start of surgery. This allowed recovery of the AER to be monitored with the test agent discontinued. In addition,

two patients were given halothane solely for the purpose of monitoring recovery. In these two patients the standard protocol was followed but the end-tidal halothane concentration was maintained constant at 1% for 10 mins. Then the halothane was discontinued leaving the patient's lungs ventilated with nitrous oxide and oxygen for a further 20 minute period. The anaesthetic concentration, in these recovery periods, could no longer be considered to be steady state. The averaged AERs were therefore sampled as frequently as possible, usually every 1024 stimuli, equivalent to every 2.8 minutes. Inspired and end-tidal gases were continuously recorded and in the case of the intravenous agents blood was sampled as frequently as possible, usually every five minutes and at the end of the recovery period.

5.4. *Effect of surgical stimulation on the AER*

In this investigation the effect of surgical stimulation on the AER was examined while the anaesthetic concentration was maintained constant. The standard protocol described in 5.1. was used except that following induction of anaesthesia and tracheal intubation halothane was added to the nitrous oxide: oxygen gas mixture to achieve a steady end-tidal halothane reading of 0.3%. A period of equilibration of at least 20 minutes was allowed. Averaged AERs were collected for up to 24 minutes prior to and 24 minutes following first incision. Assessments of pupil size and whether sweating or tears were present were made at frequent intervals. Relevant events such as, catheterisation, time of first incision were noted. Averaged AERs to 2048 stimuli, equivalent to 5.7 minutes were made continuously.

5.5. *An AER indicator of 'awareness'*

5.5.1. *Assessment of 'awareness'*

In two clinical situations, described in 5.5.2. and 5.5.3., the AER was examined in lightly anaesthetised patients in whom the isolated foream technique described by Tunstall (1977) was used to assess awareness.

This technique required that immediately following the induction of anaesthesia a pneumatic tourniquet was inflated on the

dominant arm to a value greater than systolic arterial pressure. The relaxant was then given via the other arm for tracheal intubation. At 2 minute intervals the patient was given a clear command, which had been discussed with them prior to the anaesthetic. They were asked to squeeze and release the experimenters fingers. A positive response was when they did both. Tetanic stimulation was applied at intervals to test that the muscles on the tourniquet side were not paralysed. After 25 minutes the cuff was deflated. Patients were questioned 24 hours later to see if they had any recall of events during anaesthesia.

5.5.2. *Investigations prior to general surgery*

These investigations took place before surgery started. The standard anaesthetic protocol (see 5.2.) was followed and the forearm was isolated as described above with pancuronium used as the relaxant in six of the seven patients. In the other patient the short acting relaxant vecuronium was used.

Following intubation of the trachea the nitrous oxide concentration in the inspired gas mixture was gradually reduced from 70% to 50% over a period of 25 minutes, or until a positive response of the isolated (or in the case of the vecuronium patient of the dominant) arm occurred, if this was sooner. Enflurane 1-2% inspired concentration was then given marking the end of the study. Traditional signs of anaesthesia were noted. Averaged AERs to 1024 stimuli, equivalent to 2.8 minutes were made continously.

5.5.3. *Investigations during Caesarian section*

In these investigations the anaesthetist administered the anaesthetic according to clinical practice and hence the anaesthetic protocol differed from the standard one described in 5.2. in a number of ways. The patients were not premedicated. They were pre-oxygenated for 3 minutes and cricoid pressure was applied for induction of anaesthesia with 4 mg kg^{-1} thiopentone. The forearm was isolated as described 5.5.1. and suxamethonium 1mg kg^{-1} was given for tracheal intubation. This was followed by pancuronium or vecuronium 0.08 mg kg-1, nitrous oxide: oxygen 50:50 and enflurane 1-2% inspired concentration IPPV until delivery. At

delivery syntocinon was given and the nitrous oxide increased to 70%. Enflurane was discontinued or reduced depending on the anaesthetist's preferred techniques and opiates were given. The traditional signs of anaesthesia were noted and the average AERs to 1024 stimuli, equivalent to 2.8 minutes were made continuously.

CHAPTER 6

ESTIMATION OF ANAESTHETIC CONCENTRATIONS

6.1. *Gases*

6.1.1. *Nitrous oxide and oxygen*

The flow meters (Rotameters) on the Boyle's anaesthetic gas machine were used to adjust the inspired gas mixture to the percentage of nitrous oxide and oxygen required. Manufacturers claim ± 2% of full scale accuracy for Rotameters, however, long term usage may impair this performance and a more realistic figure is ± 4% (Waaben et al. 1980). Variations of this order are of no importance to the work in the thesis for 2 two reasons:- a) they are small compared to the concentration of the inspired nitrous oxide (70%), and b) because of the within-patient design of the studies. It was not possible to use the same anaesthetic machine for every patient but the same machine was used throughout an investigation on a particular patient so that the same concentration of nitrous oxide and oxygen were delivered throughout that session. All of the investigations in the thesis are based on within patient comparisons. For instance, in the comparison between the six general anaesthetic agents (5.3.) the effects of incremental changes in the various anaesthetic agents added to a constant background concentration of nitrous oxide is the feature of interest. The effects on the auditory evoked response variables were represented by straight lines: the slopes of which were further analysed. Variations in the nitrous oxide concentration could only affect the difference between patients in the intercept of the straight lines they would not affect the slopes and hence would not influence the interpretation of the data.

6.1.2. *Carbon dioxide*

The end-tidal carbon dioxide was measured continuously at A in Fig.6.1 using a side-stream infra-red analyser (Godart 17070, for the halothane, enflurane and etomidate studies described in 5.3.). A flow rate of 500 ml min^{-1} was used to sample the gas. This would

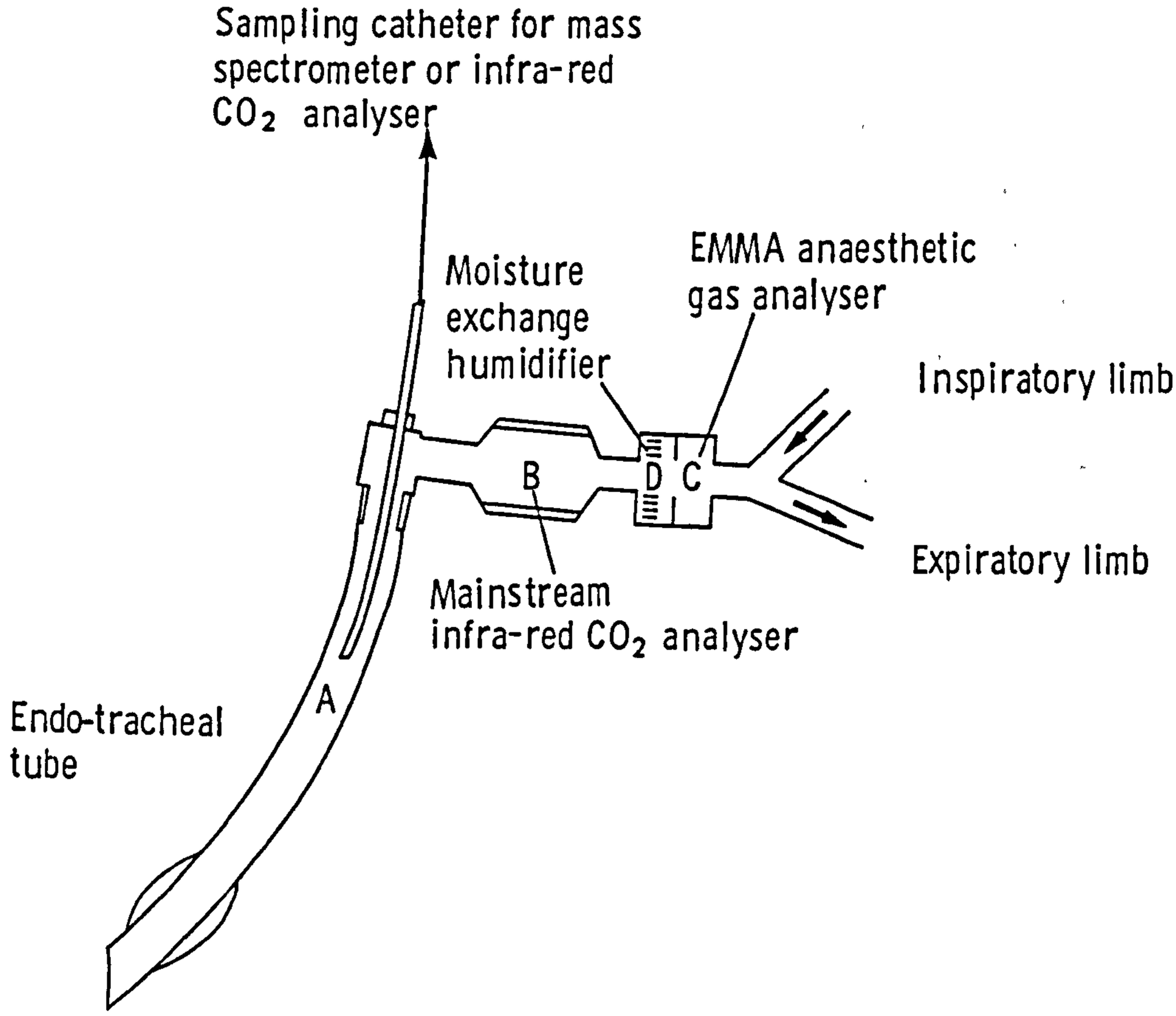


Fig.6.1. Anaesthetic circuit and gas sampling system. A, B, C and D indicate points in the circuit where various instruments were attached.

not affect the concentration of the gases breathed by the patient. For all other studies end-tidal concentration was measured continuously at B (Fig.6.1.) using a mainstream infra-red analyser (Hewlett Packard 47210A). For both instruments corrections were made for the effects of nitrous oxide. The devices were checked using calibration gas mixtures (Air Products). The 90% response time of these measuring devices was less than 500 ms.

6.1.3. *Halothane and Enflurane*

A quadrupole mass spectrometer (Ohmeda) was used to make continuous measurements of inspired and end-tidal halothane or enflurane concentrations during the general anaesthetic (5.3.) and surgical stimulation studies (5.4.). The sensor was positioned in the endotracheal tube at A (Fig.6.1.). Halothane was measured at mass number 197 and enflurane at mass number 51. The 5-95 % response time of this instrument is 800 ms. The respiratory rate was controlled so as not to exceed 15 breaths per minute ensuring that the end-tidal concentration was clearly recorded. This instrument was calibrated using a standard gas cylinder before attachment to the patient. The calibration was checked at intervals during the study.

The standard gas cylinder was prepared by evacuating a cylinder and adding a measured amount of liquid anaesthetic agent (using a syringe). Air was allowed to enter the cylinder and then it was filled with nitrogen to a pressure of 11 bar. The cylinder was thoroughly mixed by rotation. The contents were then measured by injecting into the sample loop of a gas chromatograph which had been calibrated using a volumetric standard.

The volumetric standard was made by evacuating a glass round bottomed flask of known volume (specially adapted by fitting it with a 3-way manometer tap). A calculated amount of liquid anaesthetic agent was added using a lambda pipette. Air was allowed to enter the flask to bring it to atmospheric pressure. A glass syringe containing 30 ml of air was then attached through the manometer connections and was used to mix the gas in the flask thoroughly. A sample of gas was removed via the syringe and this was used to calibrate the gas chromatograph. (Triplicate reading had to agree to the second decimal place otherwise the procedure

was repeated). The calculation of the concentration of the volumetric standard (%) when a given volume v is added is as follows:-

$$\frac{v * SG * 22.414 * T * 760 * 100}{MW * V * 273 * P} = \%$$

$$X = \frac{SG * 22.414 * T * 760 * 100}{MW * 273}$$

$$\frac{X * v * T}{P * V} = \%, \qquad v = \frac{\% * P * V}{X * T}$$

v = volume added (ml)

V = volume of flask and syringe (l)

P = barometric pressure (mmHg)

T = temperature

SG = specific gravity (g ml^{-1})

M = molecular weight

For enflurane X = 51.4064, MW = 184.5, SG = 1.52

For halothane X = 59.1105, MW = 197.4, SG = 1.4525

For isoflurane X = 51.4064, MW = 184.5, SG = 1.4961

6.1.4. *Enflurane and Isoflurane*

The EMMA (Engström) was used to make continous measurements of inspired and end-tidal enflurane or isoflurane concentrations during the Caesarian section (5.5.3.) and general anaesthetic studies (5.3.). The gas was sampled at C in Fig.6.1. and because this instrument is sensitive to water vapour a condenser humidifier was positioned at D according to the manufacturer's instructions. To ensure that the true end-tidal concentration was recorded the respiratory rate was controlled so as not to exceed 15 breaths per minute. In this situation the 5-95 % response time for this instrument is 2.2 seconds for these gases (Luff and White personal communication). The calibration of the instrument was checked against the standard gas cylinders.

6.2. *Intravenous agents*

6.2.1. *Etomidate*

Etomidate was analysed by high performance liquid chromatography (HPLC), using a method described by Ellis and Beck (1982).

A 10 ml sample of whole blood was collected into a tube containing 10 µl of saturated potassium fluoride to inhibit esterase activity. The serum was separated by centrifugation and stored at -20 °C prior to assay. 200 µl of a propoxate internal standard (4 µg ml^{-1}) was added to 2ml of serum and the sample was extracted with 10ml of pentane by vortex mixing for 30 seconds. After centrifuging at 1500 x g for 5 minutes the upper organic layer was transferred to a 10 ml conical centrifuge tube. The sample was evaporated to dryness at 40-45 °C in a water bath under a stream of nitrogen and the residue was dissolved in 200 µl of the mobile phase. 100 µl of this extract was injected onto the HPLC column.

A 5 µm ODS-Hypersil reverse phase column (25 cm x 14.6 mm internal diameter) was used. The mobile phase was 40% acetonitrile (HPLC Grade) and 60% ammonium acetate 0.2 M run at a flow of 1 ml min^{-1}. Uv detection was at 248 nm: lower limit of detection 0.01 µg ml^{-1} serum.

6.2.2. *Althesin*

The steroid alphaxalone, the active component of Althesin, was analysed using gas liquid chromatography (GLC).

A 10ml sample of whole blood was collected into a heparinised tube. The plasma was separated by centrifugation and stored at -20 °C prior to assay. 10 µl of the internal standard 2β-n-butoxy alphaxalone (100 µg ml^{-1}) and 0.5 ml of 0.5M phosphate buffer pH 11.4 were added to 1 ml of plasma and the mixture extracted with 10ml of diethyl ether. After shaking for half a minute the ether layer was separated and evaporated to dryness in a conical tube. The residue was dissolved in 0.2 ml of heptafluorobutyrylimidazole (2%) in toluene then heated at 55 °C for 10 minutes in a stoppered tube. Excess reagent was removed by vortexing for one minute with

0.5ml of 0.1M phosphate buffer pH 7.4, followed by the addition of 0.5ml of toluene. After centrifugation, 2 µl of the upper layer was taken for injection onto the GLC column. For calibration purposes 1 ml aliquots of human blank plasma with standard alphaxalone solution (in ethanol) added to give the required concentration range were treated as above.

Alphaxalone was analysed using a F33 chromatogram (Perkin Elmer) with electron capture detection. The 2m x 3mm glass column was packed with 2% Dexsil on G.C.Q. 100-120 mesh and maintained at 245 °C. The carrier gas was 90% argon, 10% methane at a flow rate of 50 ml min^{-1}. The lower limit of detection of this technique is 0.02 µg ml^{-1} plasma.

6.2.3. *Propofol*

Propofol was analysed using HPLC according to the method of Plummer (1987).

A 5ml sample of whole blood was collected into a potassium oxalate tube and stored at 4 °C to await assay. 20 µl of a thymol internal standard (1 $mgml^{-1}$ in methanol) and 1ml of 0.1M potassium dihydrogen orthophosphate were added to 1 ml of whole blood and the mixture extracted with 5ml cyclohexane (spectroscopic grade). The mixture was rotary mixed for 20 minutes and the phases then separated by centrifugation. 4.5 ml of the cyclohexane layer was taken and 50 µl of 0.2 M tetramethyl ammonium hydroxide (1.5ml of a 25% methanolic solution ex Fluka diluted to 20ml with absolute ethanol) was added. The cyclohexane phase was evaporated to dryness at ambient temperature under a gentle stream of nitrogen. The residue was dissolved in 250 µl of the mobile phase and a 100 µl aliquot of this extract was injected onto the HPLC column.

A 3 µm ODS-Hypersil reverse phase column (10 cm x 5 mm internal diameter) was used. The mobile phase was Acetonitrile:water: orthophosphoric acid (85%) in the proportions 60:40:0.2 at a flow of 1.5 ml min^{-1}. Detection was by fluorescence (SFM 23, Kontron, U.K.) with excitation at 276 nm and emission at 310 nm. The lower limit of detection was 0.1 µgml^{-1} of blood.

CHAPTER 7

AER RECORDING AND ANALYSIS

7.1. *Electrode placements*

Three channels of EEG were recorded from silver-silver chloride disc electrodes attached to the scalp at the following sites :- 1) vertex and left mastoid 2) vertex and right mastoid and 3) vertex and inion. A chin or forehead electrode was used as the earth. Prior to attachment of the electrode using either collodion glue or adhesive tape, the skin was swabbed firmly with alcohol, to reduce the electrical impedance. An impedance less than 5 Kohm between each pair of electrodes was considered acceptable.

On numerous occasions the AERs recorded from these three pairs of sites were compared. The early cortical responses were superimposable in practically all cases. In agreement with the literature (see 4.2.1.), in conscious subjects or in patients not adequately paralysed, the vertex to mastoid electrode channel proved more susceptible to post-auricular muscle artefacts. An example is shown in Fig.7.1. The early cortical variables were therefore derived from the vertex to inion channel. However the vertex to mastoid channel was used for the brainstem variables as it resulted in better definition of the brainstem waves, in particular of the II/III complex (see Fig.7.2.) and wave I was occasionally clearer. The stimulus was presented binaurally and there was no difference between recordings from right or left mastoids.

7.2. *Amplifiers*

The three channels of EEG signals were amplified by 100,000 times. One vertex to mastoid channel and the vertex to inion channel were recorded with a filter bandpass of 25-3600Hz onto an FM tape recorder (Racal, Store 4). This wide bandwidth allowed subsequent analysis of both brainstem and early cortical AERs from the same

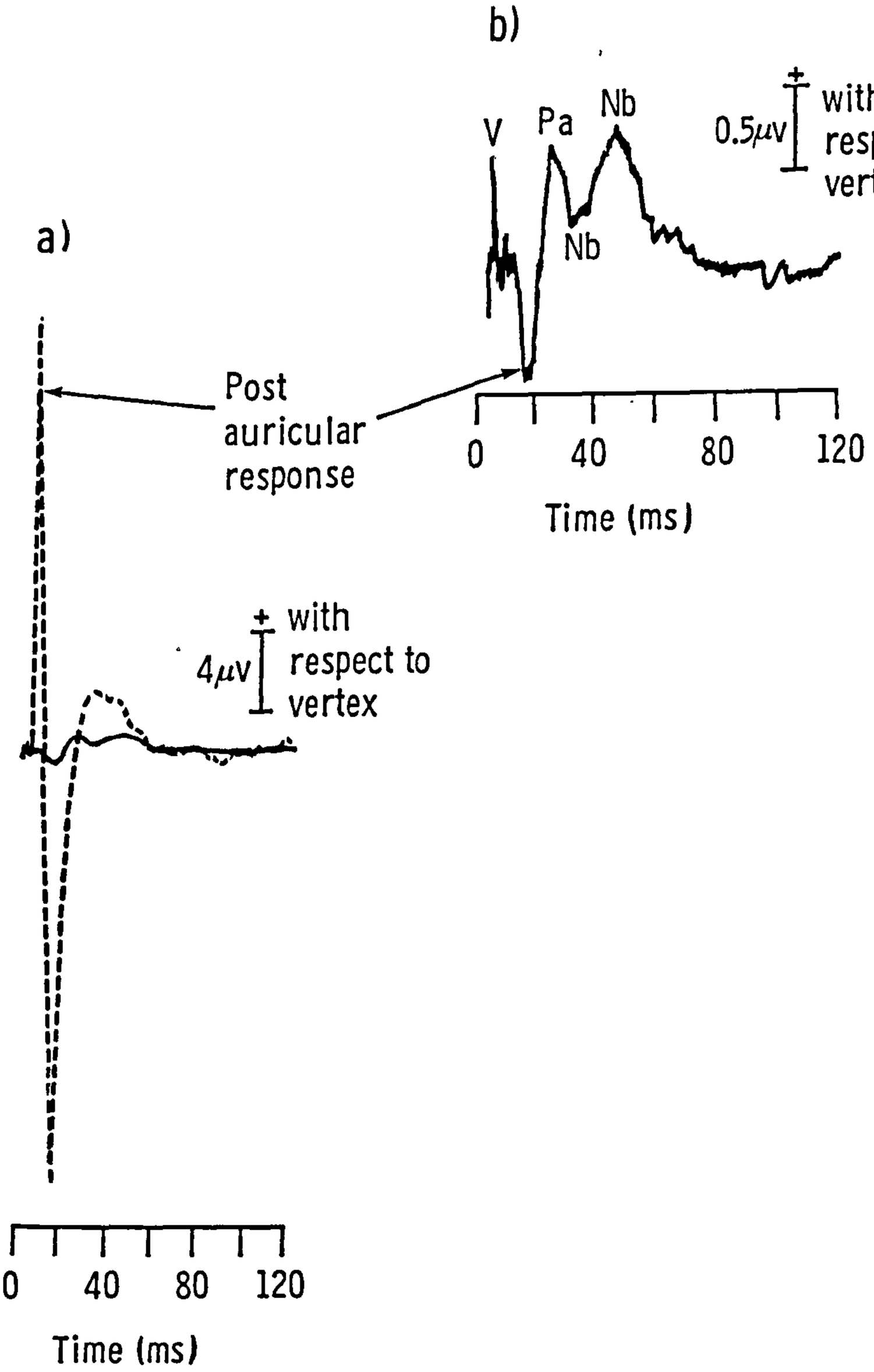


Fig.7.1. Comparison of electrode placements for recording the early cortical response. a) Recordings from vertex and mastoid ----- compared to vertex and inion ——. b) Recordings from vertex and inion (enlarged).

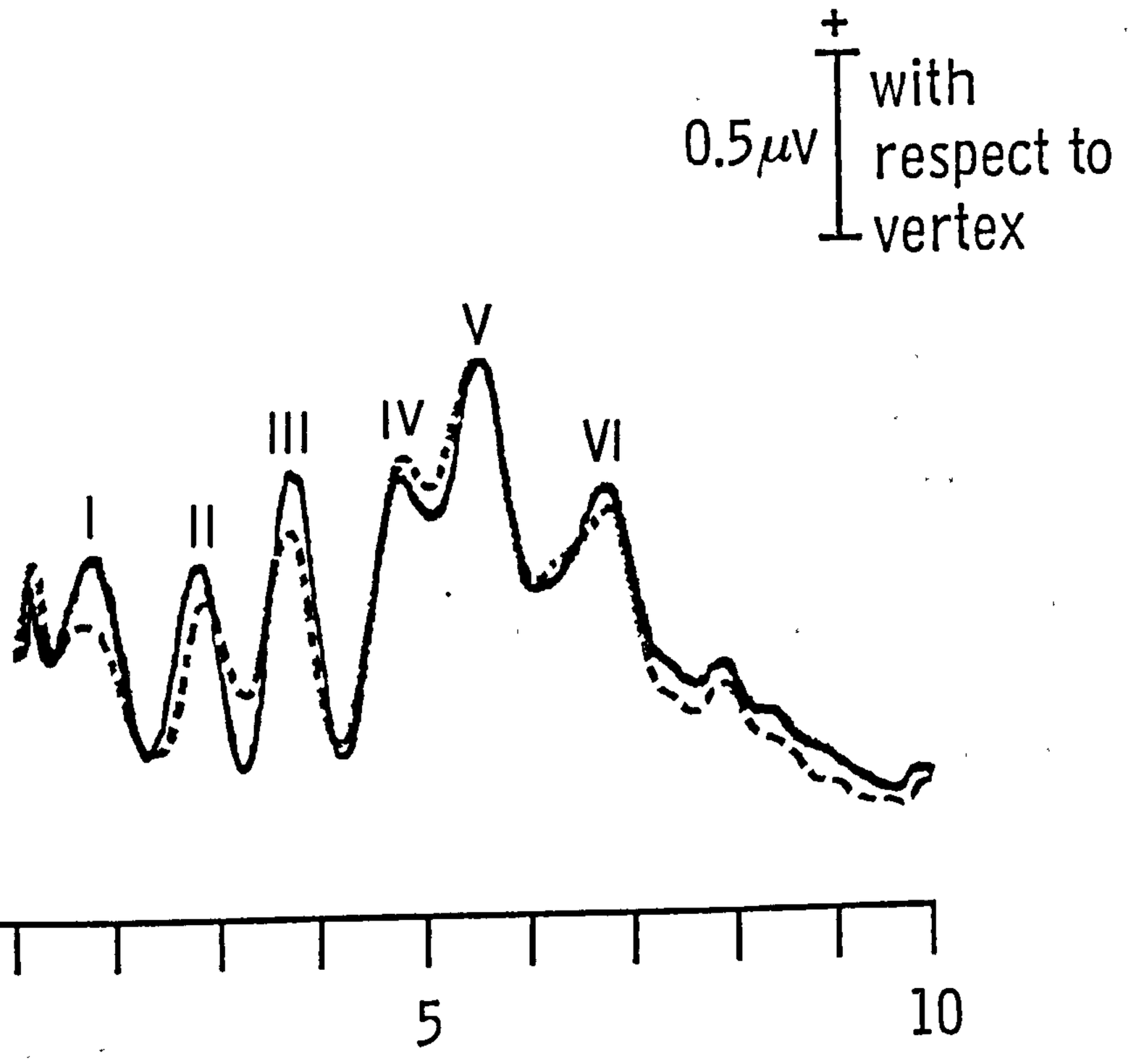


Fig.7.2. Comparison of electrode placements for recording the brainstem response. Recordings from vertex and mastoid —— compared to vertex and inion ------.

channel if required. The other vertex to mastoid channel was recorded onto FM tape with a filter bandpass of 0.5 to 100Hz for subsequent inspection of the spontaneous EEG.

In the early studies, namely the effects of halothane, enflurane and etomidate on the AER described in 5.3., the amplifiers from a Specialised Laboratory Equipment 10/8 polygraph were modified to make the recordings. For all subsequent studies a purpose built amplifier with the same amplification and filter characteristics was used.

In the study in which the effect of surgical stimulation on the AER was examined (described in 5.4.) 10 Kohm resistors were fitted into the electrode leads 10 cms from the electrode itself. Isolating the equipment in this way protected the patient from diathermy burns and the amplifiers from being overloaded. This precaution was unecessary during the Caesarian section studies (described in 5.5.2.) as diathermy was not used in these cases.

7.3. *Stimulus*

7.3.1. *Production of click stimulus*

A click stimulus was produced by applying a 500 μsec unidirectional rectangular wave pulse (Pulse generator; Global Specialities Corporation 4001) to acoustically shielded headphones (Telephonics, TDH 39P). This gave a binaural rarefaction click with a dominant frequency of 1KHz, 75dB above the average hearing threshold of the normal population. The stimulus presentation rate of 6 per second was chosen, this being the rate generally used (see literature review 4.2.2.). No formal investigation has previously been carried out to determine the optimal stimulus presentation rate to produce the early cortical response. A small investigation to determine whether larger and less variable responses could be obtained with a slower stimulus presentation rate was therefore carried out in the laboratory. The time to collect an average was kept constant, as in this particular clinical application extending the averaging time would be a disadvantage. This meant that the number of stimuli presented had to be adjusted.

7.3.2. *Effect of stimulus presentation rate/number (constant time period)*

In four resting volunteers the coefficient of variation of the latencies and amplitudes of waves V, Pa, Nb, Pb, Nc produced by stimulus presentation rates of 0.37, 0.75, 3 and 6 per second were compared. The time to collect an averaged AER was kept constant at 2.85 minutes and so the numbers of responses contributing at each of these rates were 64, 128, 512 and 1024 respectively. In this context, it is appropriate to examine the coefficient of variation, which is the standard deviation divided by the mean, as an increase in the amplitude of a wave with an accompanying increase in the standard deviation (S.D.) could have no advantage over turning up the gain on the amplifiers. In each of two sessions three averaged responses were collected at each rate/number combination.

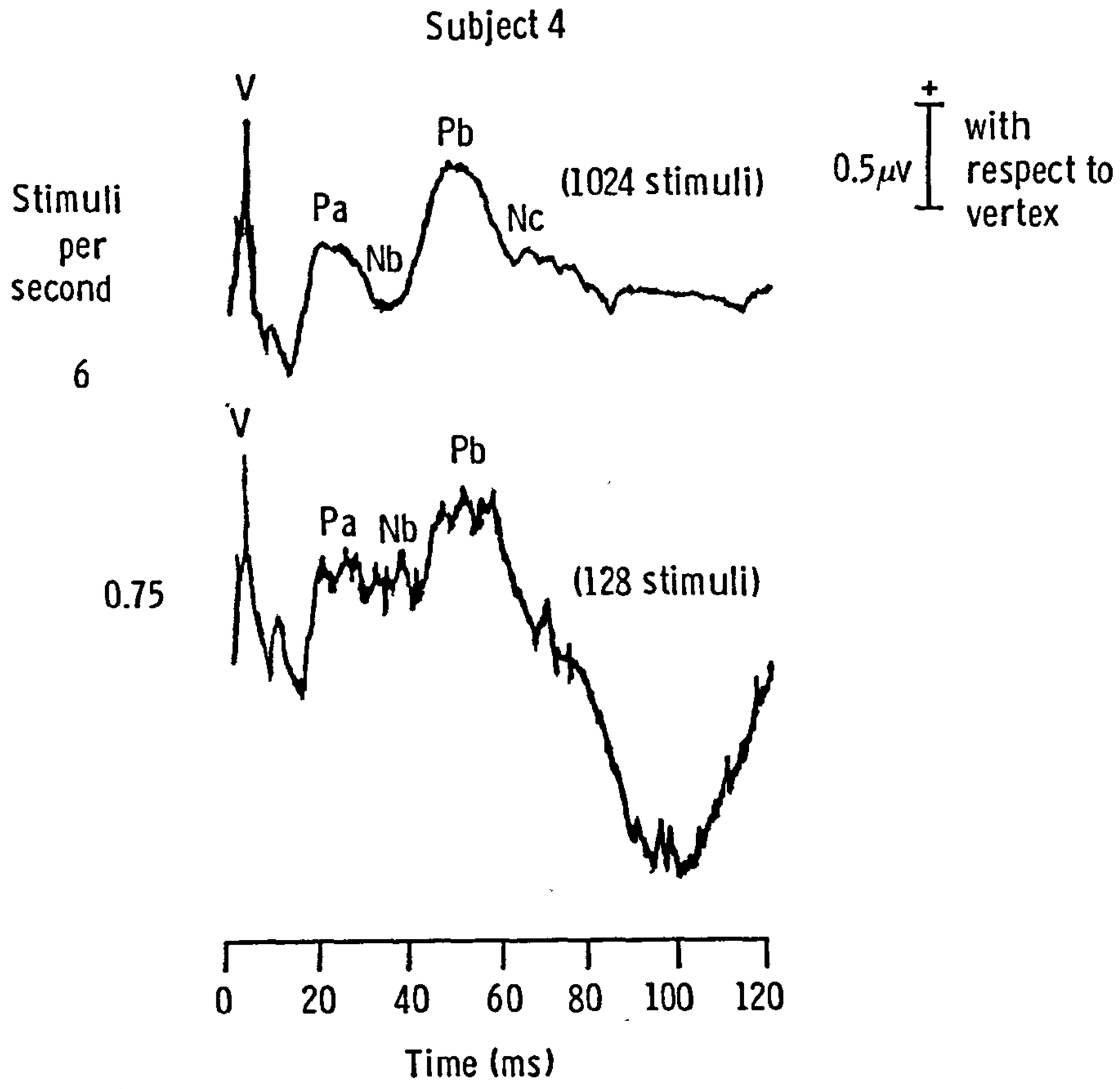
No particular rate/number combination emerged as favourable for increasing the amplitudes or reducing the variability of the early cortical waves. From the three-way analysis of variance, the stimulus presentation rate/number variable had no significant effect on latencies. The amplitudes of the waves were significantly increased at the slower rates (Table 7.1.) but in the case of Pa and Nb the standard deviations were also higher with the result that there was no consistent improvement in the coefficients of variation. In the cases of Pb and Nc amplitude decreasing the rate did appear to improve the coefficient of variation. However, in one subject S4 whose AERs are shown in Fig.7.3. Pa and Pb were not very well defined at the slower rates of 0.37 and 0.75 per second, perhaps on account of the small number of responses contributing to the average. A minimum of 512 responses is probably necessary for a reasonable average early cortical response. On the other hand, in another subject S3 whose AERs are also shown in Fig.7.3. waves Pb and Pc tended to merge at the faster rates of 3 and 6 per second. This re-affirmed the view that rates faster than 6 per second would not be suitable.

The brainstem waves were most clearly defined at the 6 per second rate (1024 stimuli). There was a progressive decrease in the standard deviation and coefficient of variation of V latency with an increase in rate (Table 7.2.). The effects of anaesthesia and surgery on the brainstem as well as the early cortical sections

Table 7.1. Effect of stimulus presentation rate/number (constant time period) on the early cortical response. Three-way analyses of variance (factors - subject, rate/number and session) were carried out on the $\log_e$ transformed data to test for significant differences in the means ($P<0.05$ used). Schweder's test for equality of variance (Schweder, 1981) was used to test for significant differences in the standard deviations (S.D.s). The means and S.D.s of the $\log_e$ transformed data and the geometric mean and coefficient of variation (cv), calculated according to Kirkwood (1979), are presented.

		Pa amplitude (μv)				Nb amplitude (μv)			
stimulus rate (Hz)	number	$\log_e$ mean	S.D.	geometric mean	cv(%)	$\log_e$ mean	S.D.	geometric mean	cv(%)
0.37	64	0.43	0.27	1.5	30	0.43	0.36	1.5	43
0.75	128	0.29	0.22	1.3	25	0.20	0.41	1.2	50
3	512	-0.02	0.16	1.0	17	-0.39	0.45	0.7	56
6	1024	-0.06	0.12	0.9	13	-0.49	0.21	0.6	22
significance		<0.001	<0.01			<0.05	<0.01		

		Pb amplitude (μv)				Nc amplitude (μv)			
stimulus rate (Hz)	number	$\log_e$ mean	S.D.	geometric mean	cv(%)	$\log_e$ mean	S.D.	geometric mean	cv(%)
0.37	64	0.67	0.30	2.0	34	0.85	0.29	2.3	34
0.75	128	0.42	0.33	1.5	39	0.53	0.28	1.7	32
3	512	-0.36	0.46	0.7	59	-0.45	0.33	0.6	39
6	1024	-0.77	0.43	0.5	53	-1.16	0.42	0.3	52
significance		<0.001	ns			<0.001	ns		



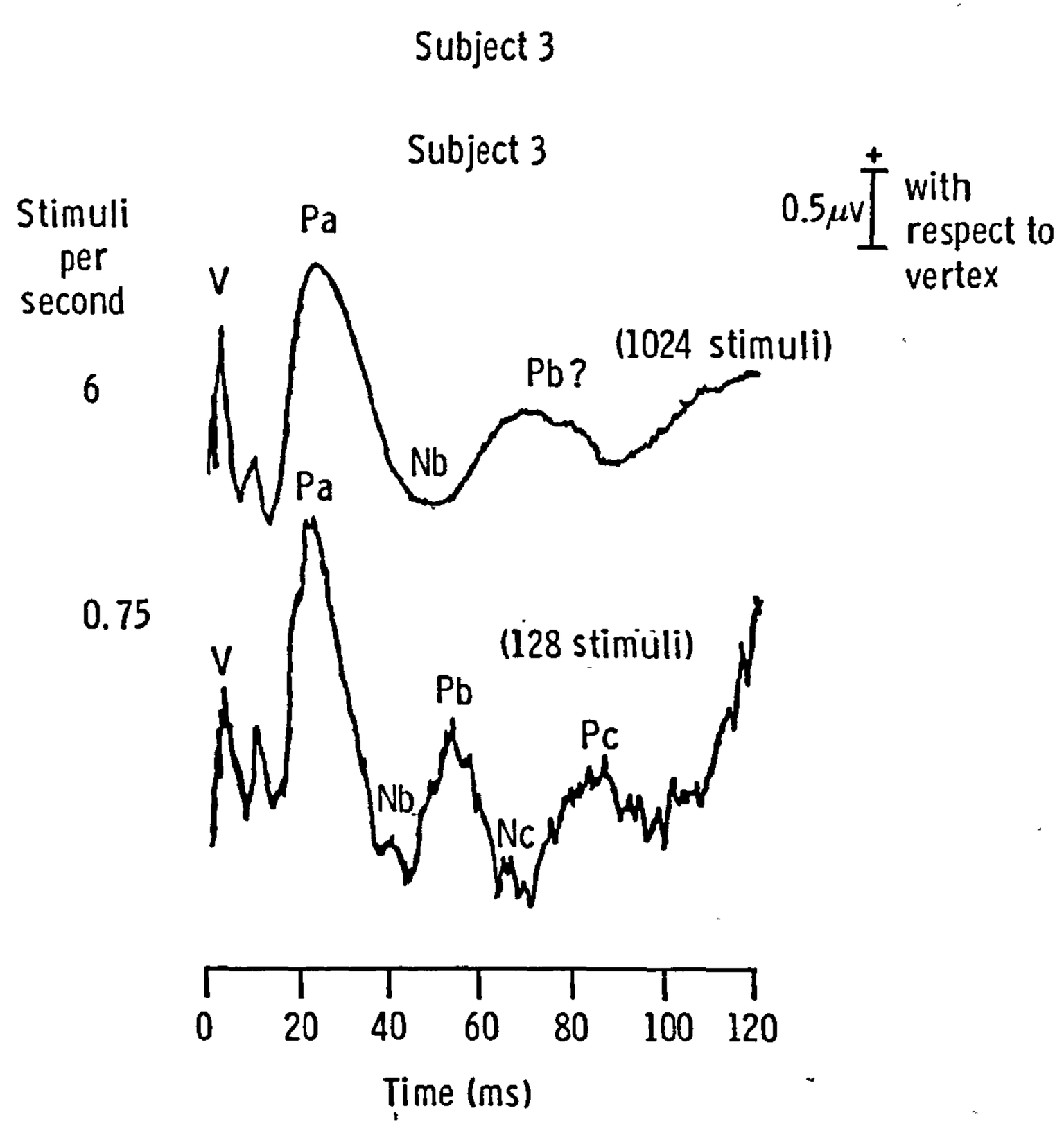


Fig.7.3. Early cortical responses of two subjects produced by stimulus presentation rates of 6 and 0.75 per second. In subject 4, Pa and Pb are not very well defined at the slower rate of 0.75 per second. In subject 3, Pa and Pb merged at the faster rate of 6 per second.

of the AER were of interest. It was therefore concluded that in this situation, where the time period over which the average is collected is to be kept constant by adjusting the number of responses contributing to it, there would be no advantage in slowing presentation rate below 6 per second.

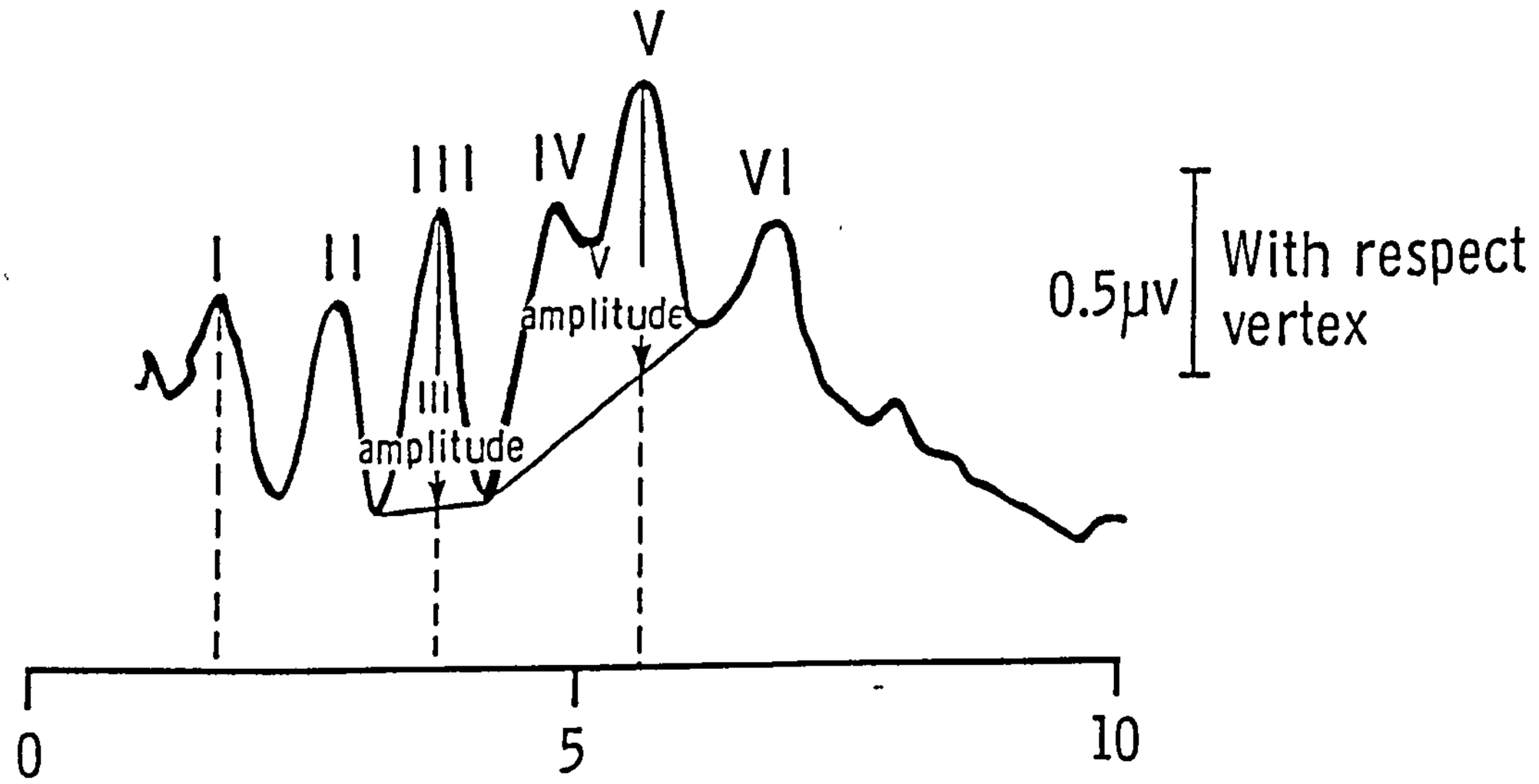
Table 7.2. Effect of stimulus presentation rate/number (constant time period) on the brainstem response. For each rate/number, the mean of the four subjects, standard deviation and coefficient of variation of V latency are given. A 3-way analysis of variance (factors - subject, rate/number and session) was carried out to test for significant differences ($P<0.05$ used) in the means. Bartlett's test for homogeneity (Armitage and Berry 1987) was used to test for significant differences in the variances.

		Wave V latency (ms)		
stimulus rate (Hz)	stimulus number	mean	S.D.	coefficient variation
0.37	64	5.7	0.09	1.5
0.75	128	5.7	0.05	0.9
3	512	5.7	0.05	0.9
6	1024	5.7	0.02	0.4
significance		ns	P<0.001	

7.4. *Extraction of AER variables*

To obtain both brainstem and early cortical responses the averaged AER to 1024 or 2048 stimuli (depending on study design see **Chapter 5**) for the post stimulus interval 0-130ms was obtained using a Datalab DL4000 averager. Values for the latency and amplitude of waves I, III, V, Pa, Nb, Pb etc. were measured on the plots (examples in Fig.7.4.). The interval between waves (interpeak intervals) I-III, I-V and III-V were calculated. In Table 7.3. the pre-anaesthetic data from the thesis, which were sufficiently artefact-free to allow reliable measurement, are compared with those recorded by Picton and his colleagues in 1974 and it is clear from the comparison that we are describing the same waves.

Brainstem response



Early cortical response

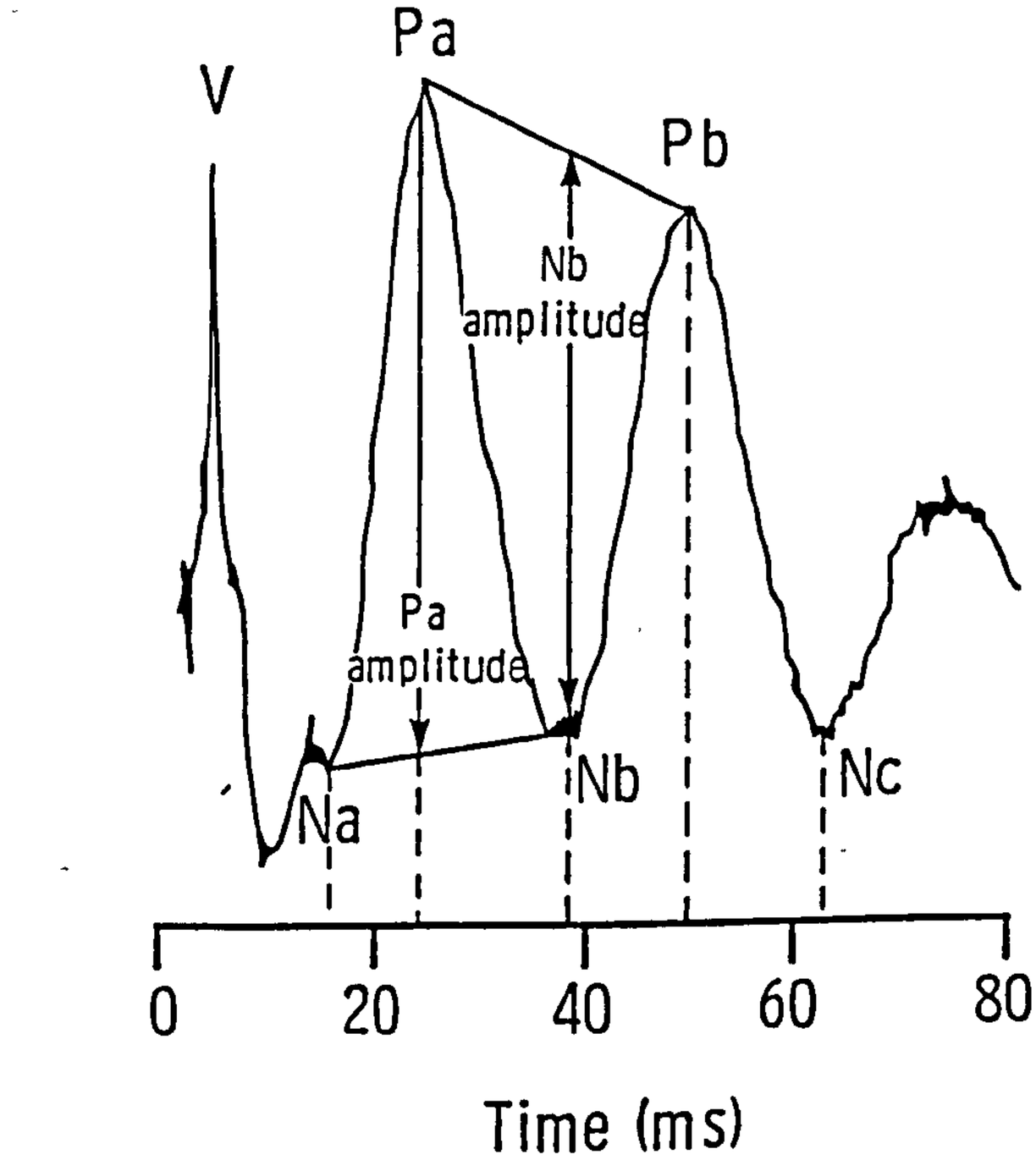


Fig.7.4. Measurement of AER latency and amplitude. Latency is measured from time zero to the peak or trough. Amplitude is the height of the vertical from the peak (in the case of a positive wave e.g. Pa) to where it bisects the line joining the two neighbouring troughs.

Table 7.3. Pre-anaesthetic values for latencies of waves I, III, V, Pa and Nb compared with the data of Picton et al. (1974).

	these studies (n = 50)		Picton et al. (1974) (n = 20)
Latency (ms)	Mean	(S.D.)	Mean
I	1.7	(0.21)	1.5
III	3.8	(0.23)	3.8
V	5.7	(0.33)	5.8
Pa	27	(2.1)	25
Nb	39	(5.8)	36

7.5. *Statistical analyses*

7.5.1. *Effect of general anaesthetics (results in Chapter 8)*

Comparisons of anaesthetic drugs with saline: For each patient each AER variable was plotted against time (see study design in 5.3.) and a slope was calculated. Analyses of variance were used to compare the mean slope of the group of patients given a particular anaesthetic drug against that of saline, using the between patient standard deviation of the slopes. ($P<0.05$ was taken as statistically significant).

Dose relationships: For each patient each AER variable was plotted against concentration (see study design in 5.3.) and a slope was calculated. The mean slope of the group of patients given a particular anaesthetic drug was tested for a significant difference from zero using the SEM of the slope for that drug. ($P<0.05$ was taken as statistically significant).

Comparison of anaesthetic drugs: Analyses of variance were used to compare the mean slopes of the AER variables against concentration of the different drugs (in units of equipotency see 12.2.3. for discussion of calculations) using the between patient standard deviations of the slopes. ($P<0.05$ was taken as statistically significant).

Changes in arterial blood pressure: The change in systolic blood pressure over the period of the study (mean of post-induction period - mean of final test period) was calculated for each patient. For a particular anaesthetic, a paired t-test was used to test whether the mean change for the group of patients given that drug was significantly different from zero at $P<0.05$.

7.5.2. *Effect of surgical stimulation (results in Chapter 9)*

Analyses of variance were carried out on each AER variable. Data from 24 minutes before incision and 24 minutes after were used. These data (before and after incision) were each divided into two 12 minute periods. First the data before and after incision were compared and then the difference between the two periods before incision with the two periods after incision; that is the surgery X period interaction was tested to see if it was significant at $P<0.05$. In this analysis the data before incision are used as a baseline to indicate the kind of change that would be expected from two consecutive 12-min periods.

Finally whether the effects of surgery were related to the patients' autonomic responses to surgical stimulation was determined. Patients were classified 'responders' or 'non-responders' and the surgery X responder interaction was tested to see if it was significant at $P<0.05$.

7.5.3. *An AER indicator of 'awareness' (results in Chapter 10)*

Extraction of mathematical criteria to distinguish 'three and two wave' AERs: Data of the 42 patients from the drug studies described in **Chapter 8** were used. Each patient contributed a pair of AERs, one following induction of anaesthesia and the other after the addition of a low concentration of the test agent (or the start of the first infusion if saline was given). The experimenter divided the AERs into two groups depending on whether there were 'three' or 'two' waves between the latencies 15 to 100 ms. The data of six patients were rejected from this analysis on account of difficulties in categorisation caused by technical problems at the time of data collection. The latencies of the 1st and 2nd positive waves Pa, Pb or Pb/Pc and the 1st, 2nd and 3rd negative troughs Na,Nb and Nc or Nc/Nd of the 36 remaing patients were entered into the discriminant analysis program. From these measurements a

formula was derived which gave the closest agreement with the experimenter's three/two wave classification. The analysis is elaborated further in Chapter 10 along with presentation of the results.

SECTION C

RESULTS

CHAPTER 8

EFFECT OF GENERAL ANAESTHETICS ON THE AER

8.1. *Introduction*

The aims of the studies described in this chapter were 1) to examine the AER variables (described in 7.4) for graded changes with increasing anaesthetic concentration of general anaesthetics (see 5.3 for protocol) and 2) to determine whether these changes were similar for different general anaesthetics.

Six general anaesthetic agents, of diverse chemical structures were tested. These were the most commonly used types of general anaesthetics at the time of the study. Three of these were inhalation and three intravenous agents. The chemical structure of these compounds are given in Fig.8.1. Etomidate is an imidazole, Althesin a steroid, and propofol a steric hindered phenol. Of the inhalation agents, halothane is a halogenated hydrocarbon, enflurane and isoflurane are halogenated ethers. They were added to the inspired nitrous oxide:oxygen mixture or to the saline infusion, following induction of anaesthesia with sodium thiopentone. Changes in the AER were observed, the effects on brainstem and early cortical responses are described separately.

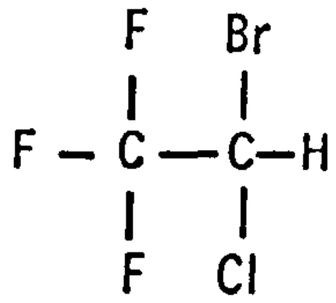
8.2. *Brainstem response*

8.2.1. *Description of changes*

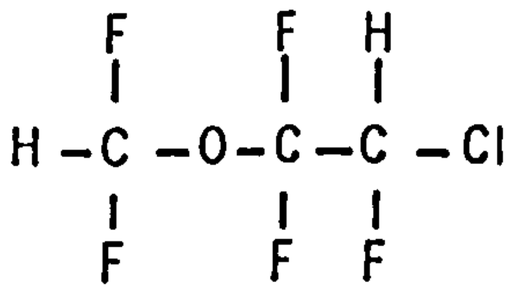
Effect of thiopentone induction: This chapter deals with the effects of anaesthetic agents at steady state, and the induction agent thiopentone was given as a bolus injection. The effect on the brainstem AERs and the subsequent recovery from the thiopentone injection was difficult to evaluate on account of the rapidly changing levels of the drug. Fig.8.2. indicates the striking changes in the EEG following thiopentone which occur over very short periods of time. A clearly recognisable brainstem response

Inhalation anaesthetics

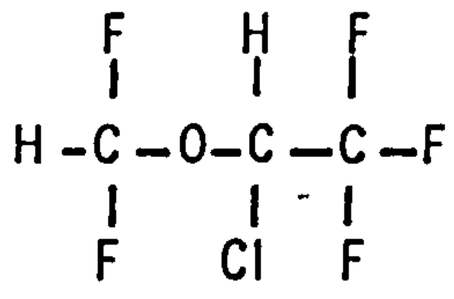
Halothane



Enflurane

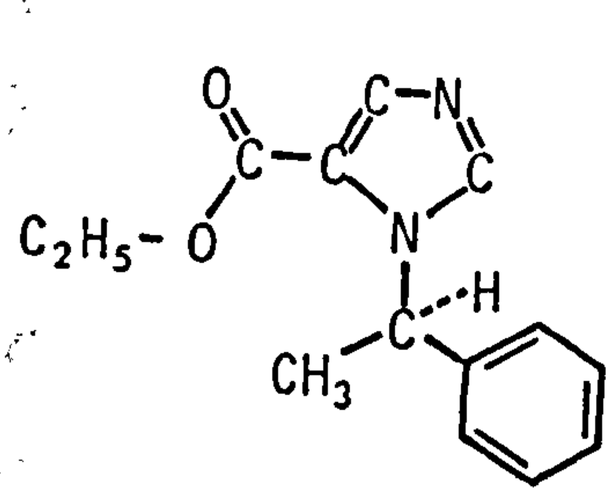


Isoflurane

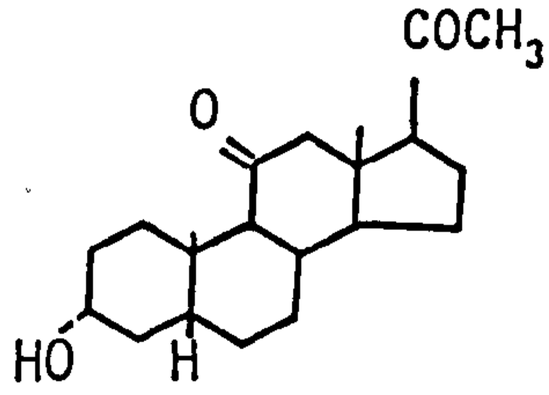


Intravenous anaesthetics

Etomidate



Althesin
(active component 3α- hydroxy alphaxalone)



Propofol

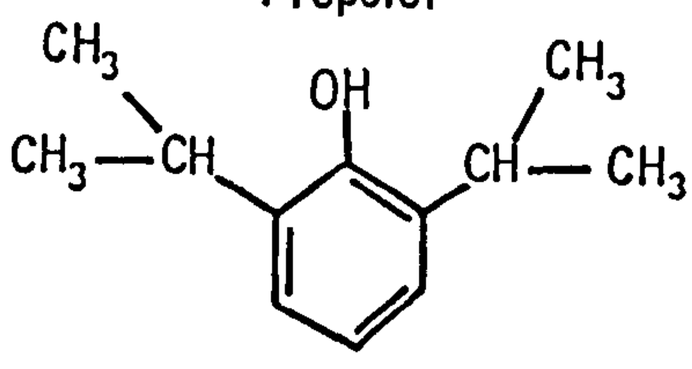


Fig.8.1. Chemical structure of the six general anaesthetics tested.

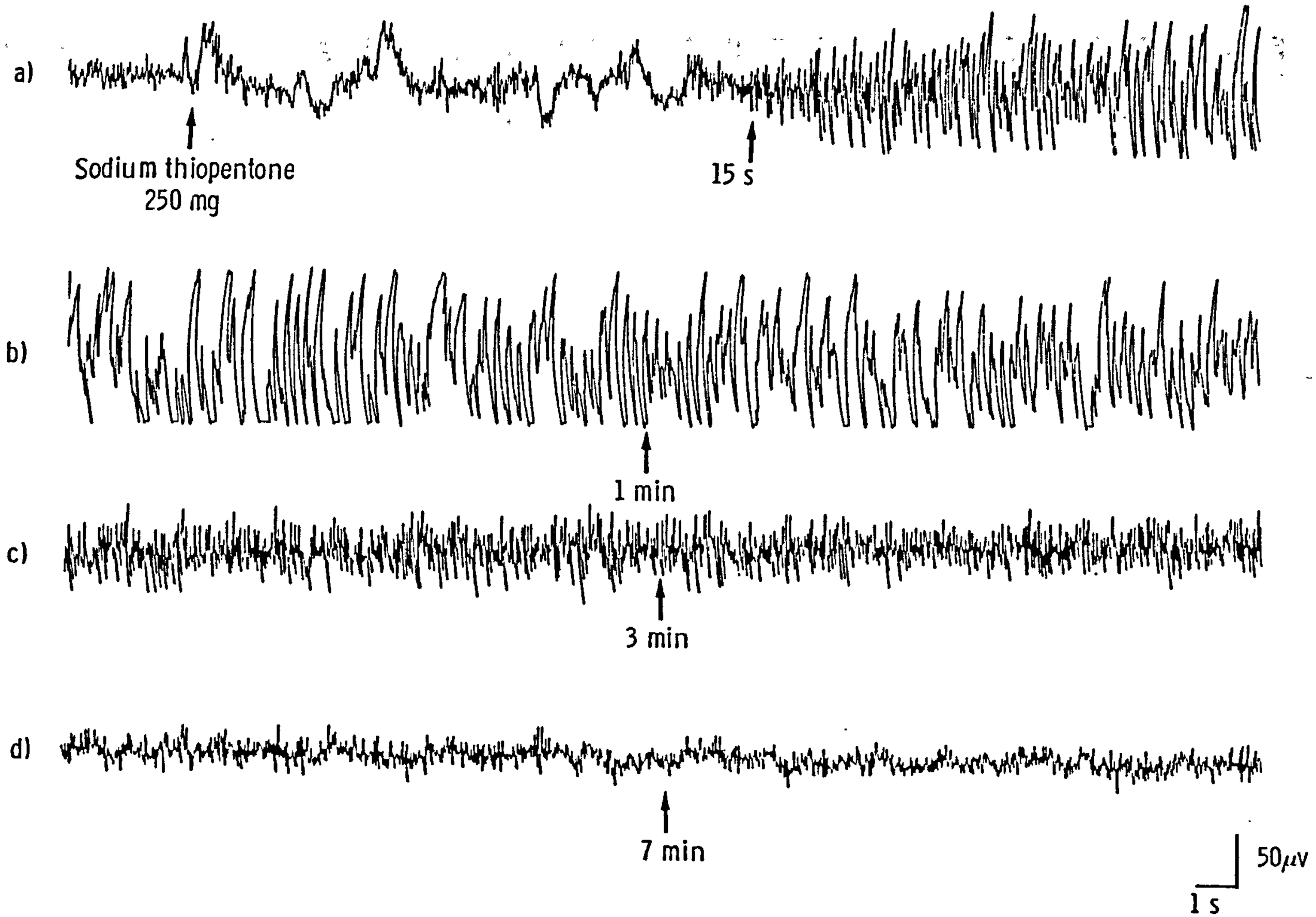


Fig.8.2. Effect of thiopentone induction on the EEG. After a delay of 15 seconds, increasing numbers of delta waves (normally associated with deep sleep) appear reaching a maximum approximately 1 minute after the injection and diminishing to pre-drug values within 6 minutes.

could not be obtained from an average to 256 stimuli. This corresponds to the maximum period over which thiopentone levels might be assumed constant. No obvious changes were noted.

Effect of general anaesthetics: The inhalational agents produced substantial increases in the latencies of the brainstem waves III and V over the period which they were administered. In contrast, the intravenous anaesthetics resembled saline in having little or no effect. Examples are shown in Fig.8.3. In the patient given enflurane waves III and V were progressively delayed as the drug concentration increased. No such changes were seen with increasing concentrations of etomidate or saline administered for an equivalent time period. The amplitudes were unchanged in all three cases.

When the inhalation agent was discontinued the changes in III and V latency were reversed, although not completely over the study period, and not in all patients. Recovery of the response was studied in 6 patients, 4 who received halothane, one who received enflurane and one who received isoflurane, over time periods ranging from 8 to 24 minutes. Two of the patients who had been given halothane showed no recovery of the brainstem components over 8 and 18 minutes. The other four patients showed some recovery of the response. The AERs of one such patient are shown in Fig.8.4. Twenty four minutes after the halothane had been turned off the end-tidal level had fallen to 0.25% but peaks III and V had still not returned to the positions when halothane was being administered and the end-tidal was 0.37%. This is in contrast to the changes in the early cortical response (described in 8.3.1.) which did return to the 0.37% value. In other words recovery of the brainstem response lagged behind that of the early cortical response.

8.2.2 *Statistical analyses - details in 7.5.*

Comparisons of general anaesthetic with saline: Using the data of all the patients, the difference between the inhalation and intravenous agents was confirmed and also that the effects of the inhalation agents were not simply time related trends.

The brainstem variables were plotted against time. To illustrate the variability between patients, the slopes for all

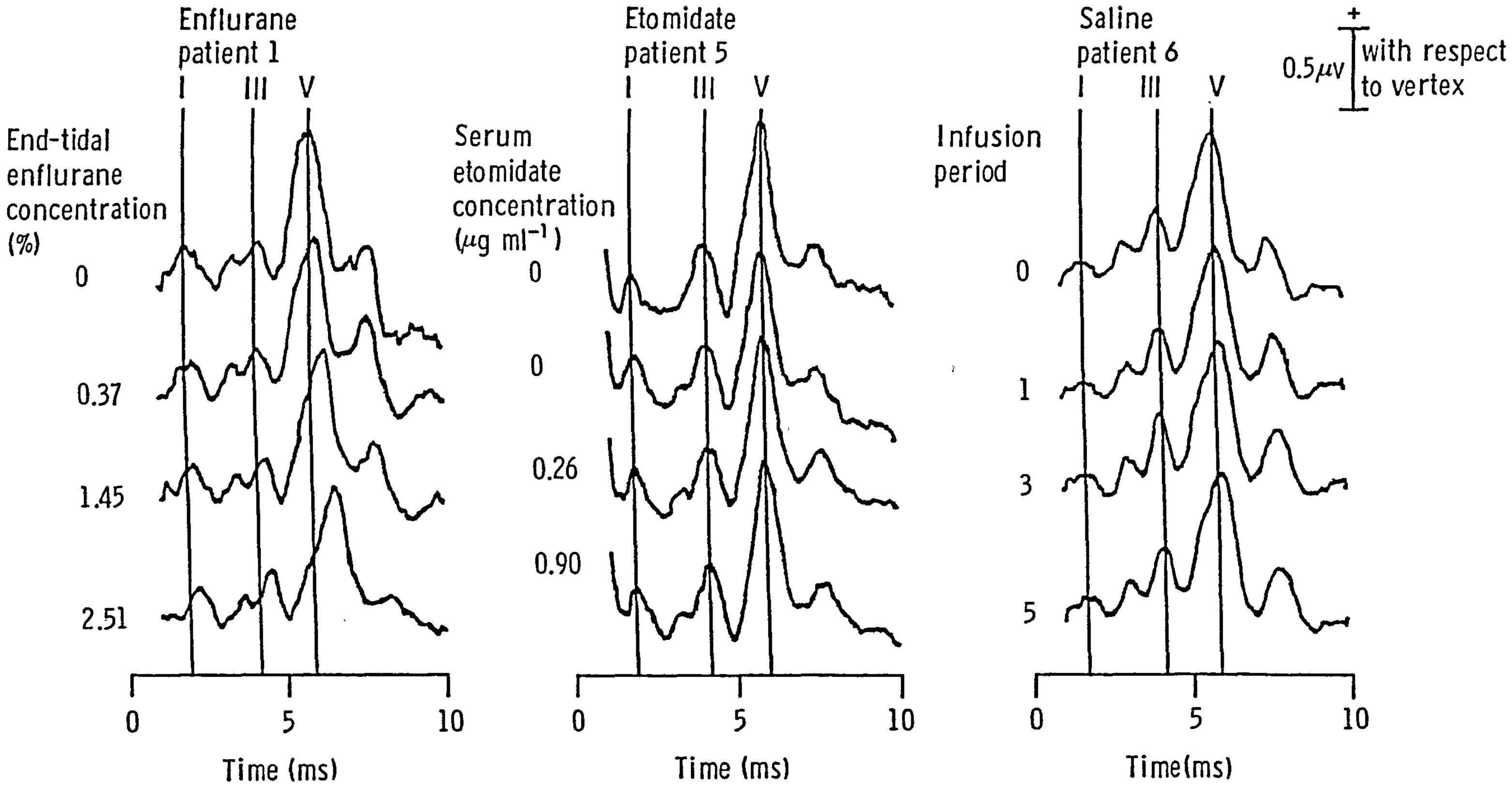


Fig.8.3. Brainstem responses in patients given a)enflurane, or b)etomidate or c)saline infusions. Vertical lines are drawn through waves I, III and V at the concentrations labelled zero, at which time anaesthesia was being maintained on 70% nitrous oxide and 30% oxygen.

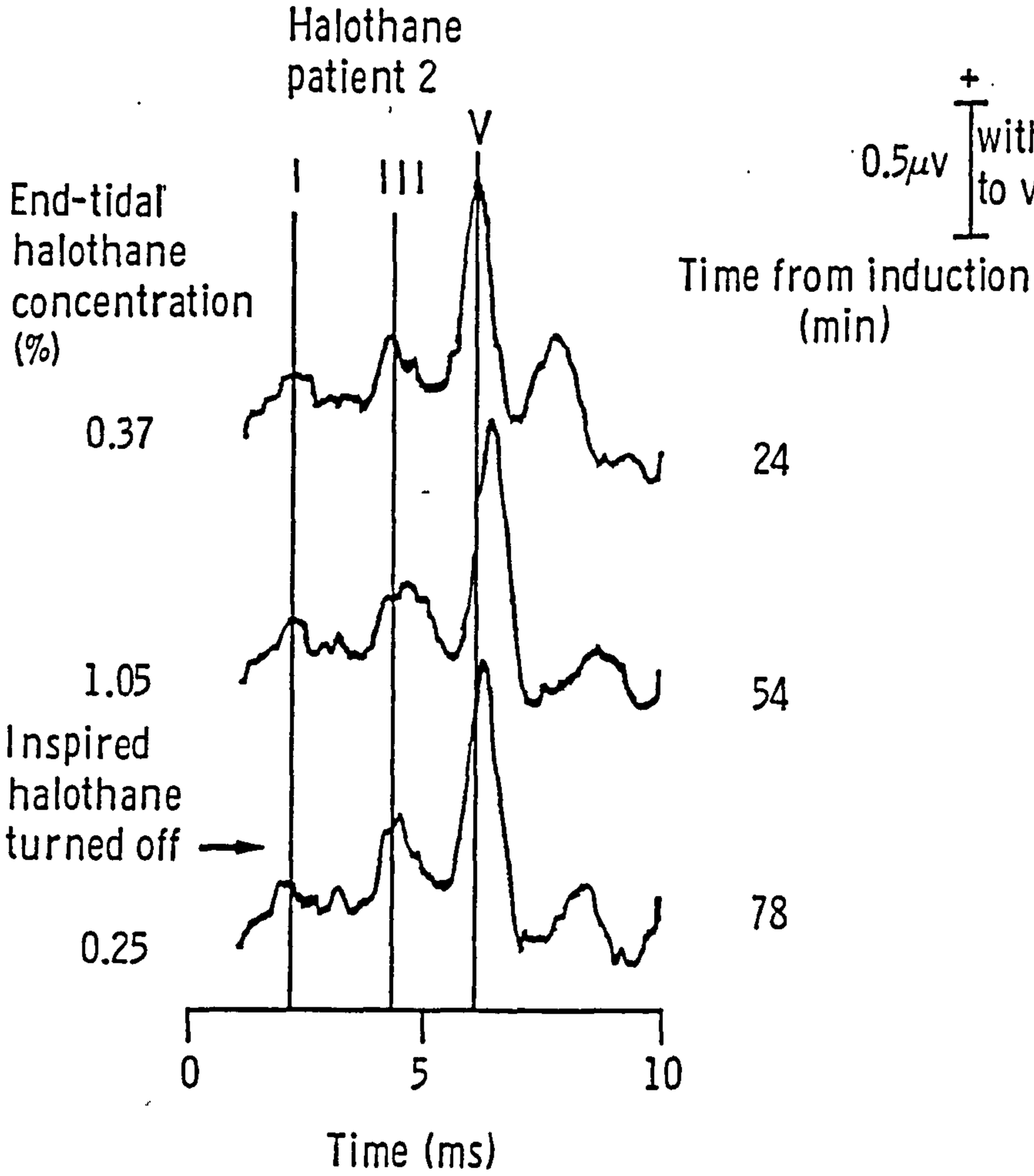


Fig.8.4. Brainstem responses of a patient in whom recovery from halothane was monitored. The halothane was turned off and the patient remained on 70% nitrous oxide, 30% oxygen. Vertical lines are drawn through waves I, III and V at the first concentration of halothane.

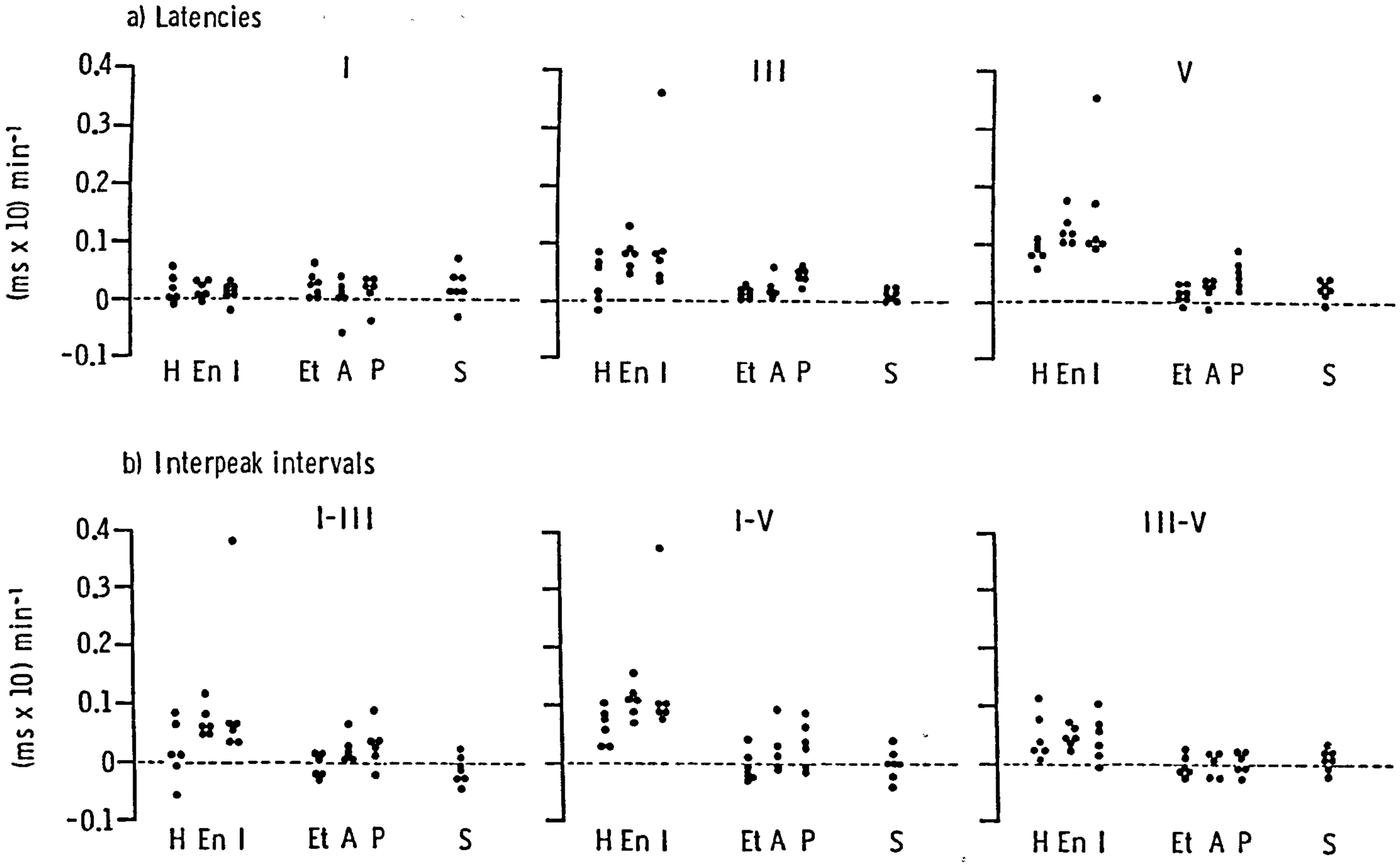


Fig.8.5. Slopes (ms x 10) against time (min) of brainstem waves I, III and V a) latencies b) interpeak intervals for individual patients. Each patient received one of the six general anaesthetics or saline (H=halothane, En=enflurane, I=isoflurane, Et=etomidate, A=Althesin, P=propofol and S=saline).

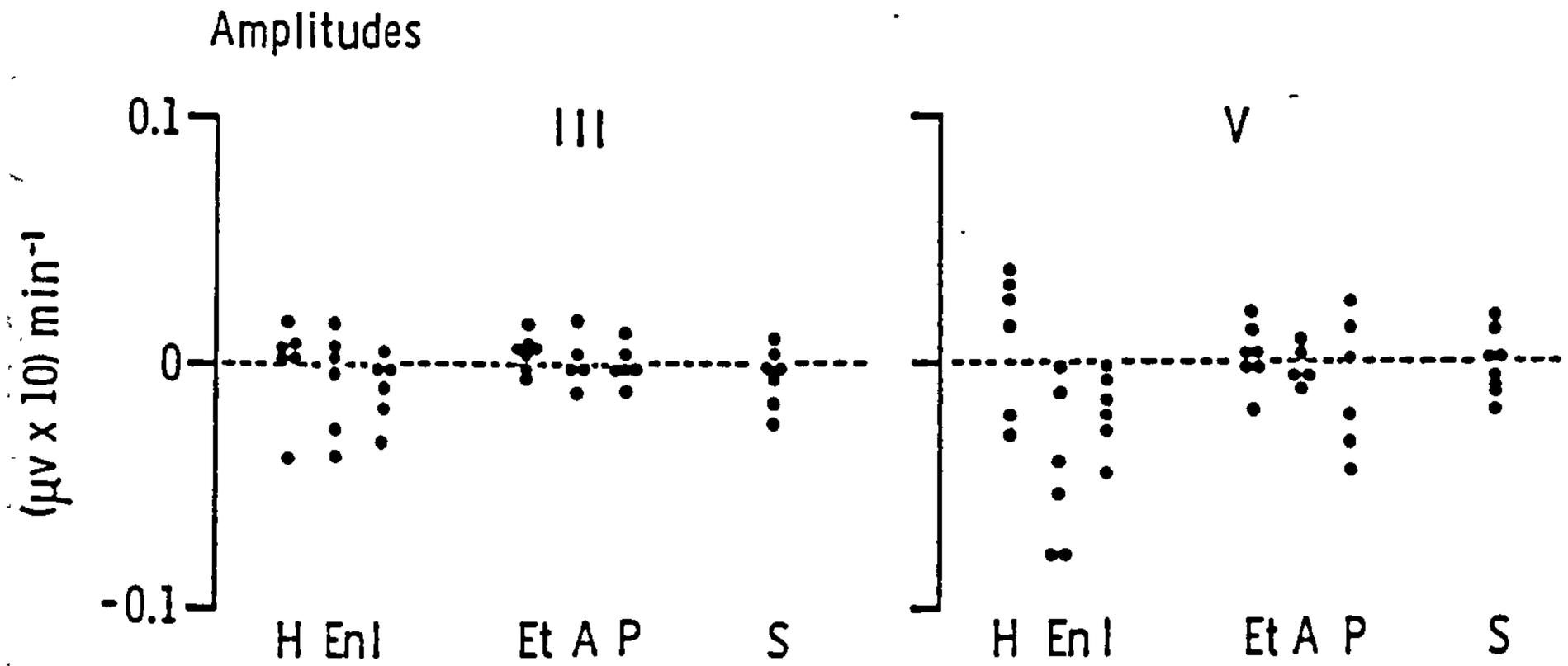


Fig.8.6. Slopes (μv x 10) against time (min) of brainstem waves III and V amplitudes for individual patients. Each patient received one of the six general anaesthetics or saline (H=halothane, En=enflurane, I=isoflurane, Et=etomidate, A=Althesin, P=propofol and S=saline).

Table 8.1. Brainstem latencies and interpeak intervals - regressions against time. Mean slopes (ms x 10) against time (min). Mean slopes that are significantly different from that of saline are indicated by * = P<0.05, ** = P<0.01 and *** = P<0.001. The pooled estimate of the between patient S.D. of the variable, derived from an analysis of variance, was used to test for differences between anaesthetic agents and saline.

		Latencies			Interpeak intervals		
		Mean slopes (ms x 10) min^{-1}					
		I	III	V	I-III	I-V	III-V
halothane	(n = 6)	0.02	0.04	0.09*	0.02	0.07*	0.05*
enflurane	(n = 6)	0.02	0.09*	0.13***	0.07*	0.11***	0.04*
isoflurane	(n = 6)	0.01	0.12***	0.16***	0.11***	0.15***	0.04*
etomidate	(n = 7)	0.02	0.01	0.01	-0.01	-0.01	0.00
Althesin	(n = 5)	0.00	0.02	0.02	0.02	0.02	0.00
propofol	(n = 6)	0.01	0.04	0.05	0.03	0.04	0.01
saline	(n = 7)	0.02	0.01	0.02	-0.01	0.00	0.01
		pooled estimate of S.D. (ms x 10) min^{-1}					
all groups	(n = 43)	0.024	0.051	0.042	0.059	0.052	0.026

six drugs and saline are shown in Figs.8.5 and 8.6. (Each datum point represents one patient given one drug or saline. The mean slope for each drug and saline are given in Tables 8.1 and 8.2.

Table 8.2. Brainstem amplitudes - regression against time. Mean slopes against time in minutes. Means that are significantly different from that of saline are indicated by *** = P<0.001. The pooled estimate of the between patient S.D. was derived from an analysis of variance and used for these comparisons.

	Amplitudes Mean slope (μv x 10) min^{-1}	
	III	V
halothane (n = 6)	0.00	0.01
enflurane (n = 6)	-0.01	-0.05***
isoflurane (n = 6)	-0.01	-0.02
etomidate (n = 7)	0.00	0.00
Althesin (n = 5)	0.00	0.00
propofol (n = 6)	0.00	0.01
saline (n = 7)	-0.01	0.00
	Pooled estimate of S.D. (μv x 10) min^{-1})	
all groups (n = 43)	0.014	0.022

The mean slopes of V latency, I-V and III-V interpeak interval against time were significantly greater for the three inhalation agents than the corresponding slopes of the saline group (Fig.8.7. illustrates this comparison for V latency). This was true also for III latency and I-III interpeak interval for enflurane and isoflurane. The mean slope of V amplitude against time was significantly less for enflurane than that of the saline group.

In the case of the intravenous agents, none of these variables had mean slopes against time which were significantly different from those of the saline group.

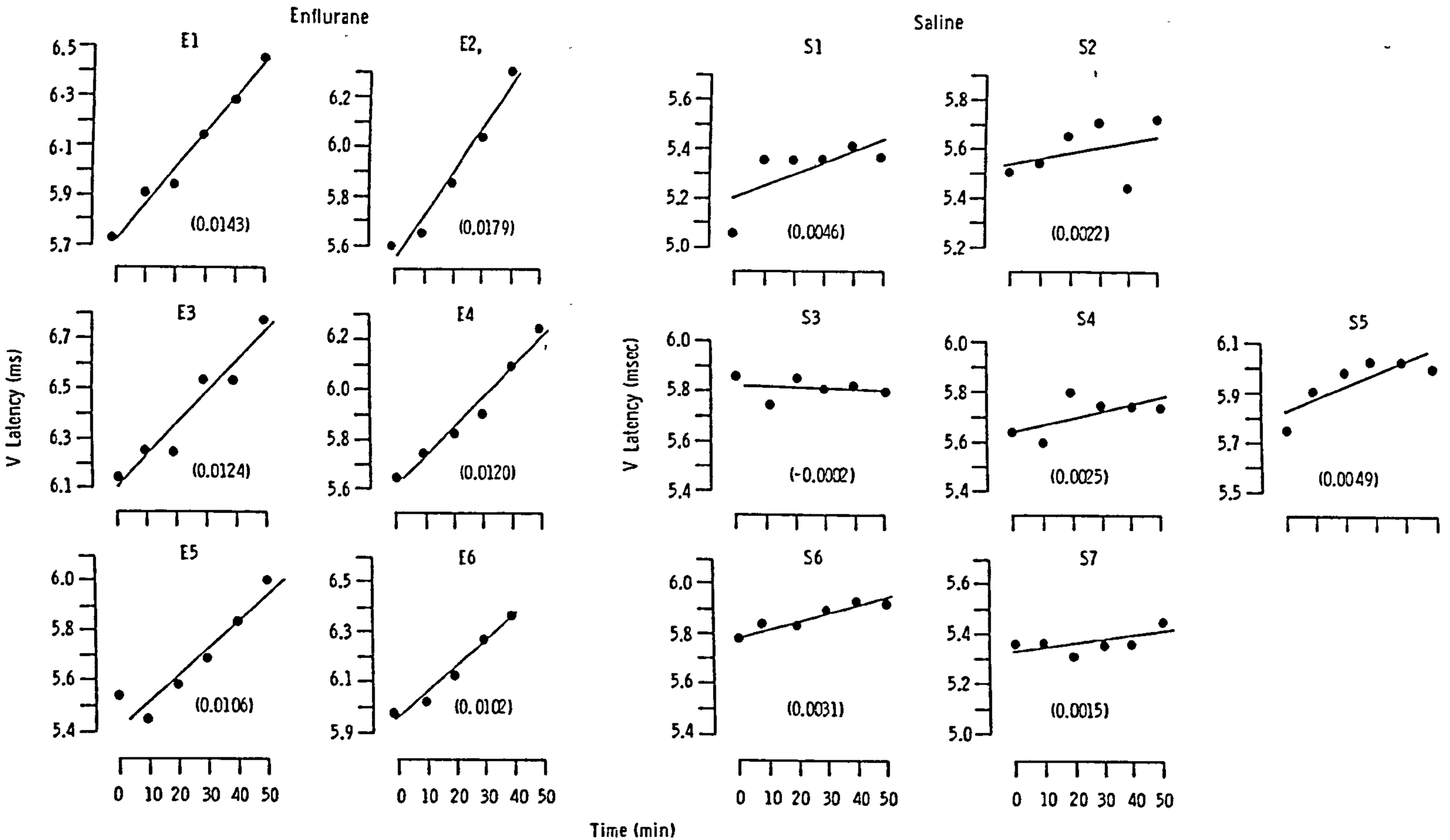


Fig.8.7. V latency (ms) against time (min) for the patients who received a) enflurane and b) saline infusions. The slope for individual patients is in brackets. The mean slope for the enflurane group was 0.0129 ms min^{-1} compared to the mean slope for the saline group which was 0.00265 ms min^{-1}. The difference was significant at $P<0.001$.

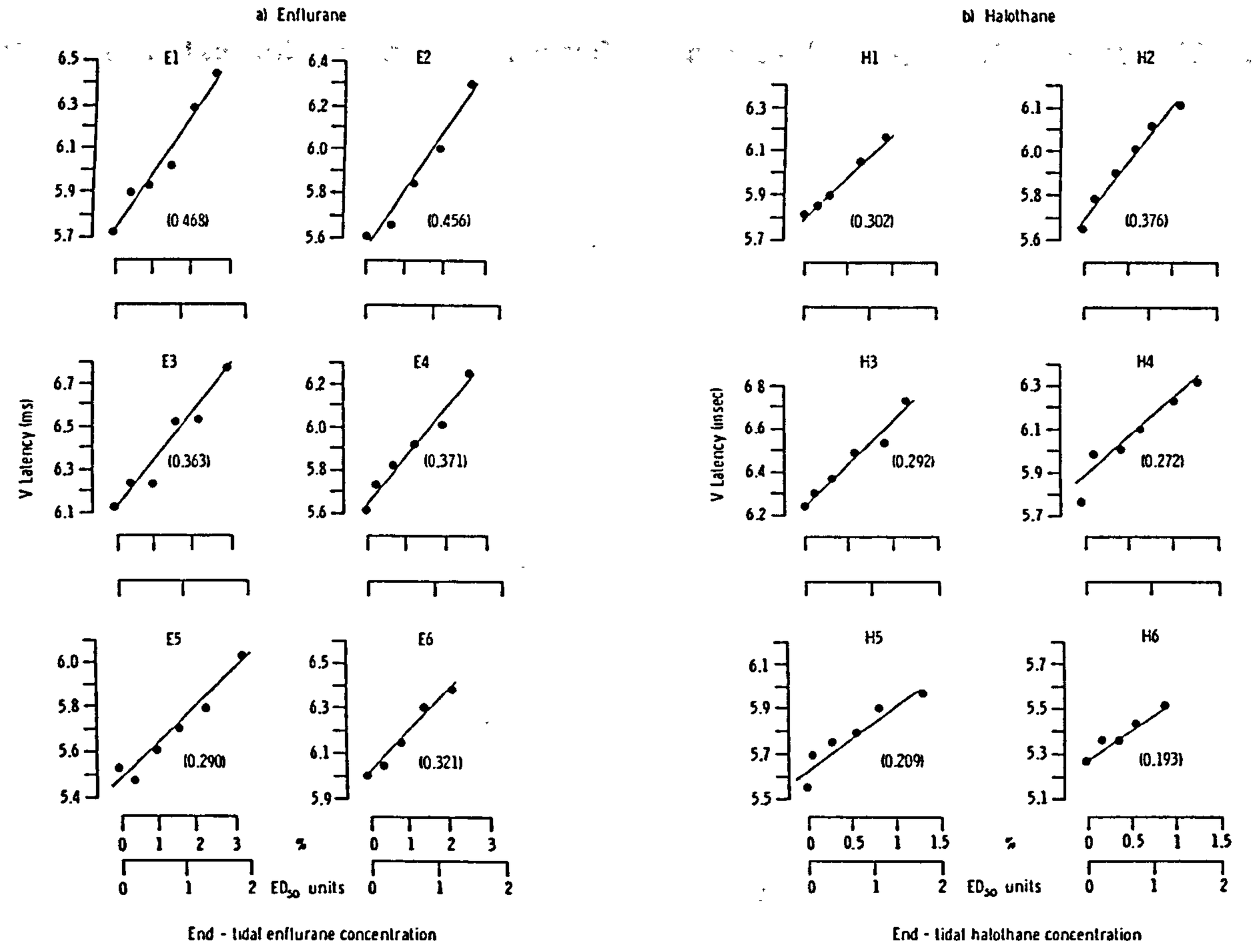


Fig.8.8. V latency against end-tidal concentration (% and beneath ED_{50} units) for patients who received a) enflurane b) halothane. The slopes (ms ED_{50} $units^{-1}$) of individual patients are given in brackets. The mean slope (ms ED50 $units^{-1}$) for the enflurane group was 0.27 and for the halothane group 0.38. These slopes were significantly different from zero ($P<0.01$) but not from one another.

Table 8.3. Brainstem latencies and interpeak intervals - regressions against concentration.
Mean and SEM of slopes (μv) against concentration (ED_{50} units). An ED_{50} unit is equivalent to end-tidal concentrations of enflurane 1.68%; halothane 0.75% and isoflurane 1.15%. Mean slopes that are significantly different from zero (SEM of individual drugs used to test this) are indicated by * = $P < 0.05$, ** = $P < 0.01$ and *** = $P < 0.001$. The pooled estimate of the between patient S.D., of the variable derived from an analysis of variance, was used to test for differences between anaesthetic agents. There were no significant differences at $P < 0.05$.

	Latencies			Interpeak intervals		
	Mean (SEM) slopes (ms. ED_{50} units^{-1})					
	I	III	V	I-III	I-V	III-V
halothane (n = 6)	0.06 (0.029)	0.13* (0.049)	0.27*** (0.027)	0.07 (0.062)	0.22** (0.042)	0.14* (0.043)
enflurane (n = 6)	0.05* (0.014)	0.25*** (0.027)	0.38*** (0.030)	0.20*** (0.024)	0.33*** (0.029)	0.13** (0.024)
isoflurane (n = 6)	0.02 (0.014)	0.26 (0.107)	0.35** (0.084)	0.24 (0.117)	0.33* (0.095)	0.10* (0.034)
pooled est. S.D.	0.050	0.171	0.132	0.191	0.153	0.085

Dose relationships. The changes in the brainstem variables produced by the inhalation agents were linearly related to end-tidal concentration. Examples are given in Fig.8.8. where V latency is plotted against the end-tidal concentration of halothane or enflurane in % and ED_{50} units (effective dose for 50% of patients, a unit of equipotency, the derivation of which is discussed in section 12.2.3.) for the patients given these agents. The mean slopes against concentration in ED_{50} units, for each anaesthetic agent, for all brainstem variables are shown in Tables 8.3. and 8.4. (converting the slopes to ED_{50} units does not affect the significance of the difference of the slope from zero.) With the exception of III latency with isoflurane, the mean slopes of III and V, I-V and III-V interpeak interval were significantly increased compared to zero. In addition the mean slope of I latency and I-III interpeak interval were significantly increased for enflurane and the mean slope of V amplitude significantly decreased compared to zero for isoflurane and enflurane.

Table 8.4. Brainstem amplitudes - regressions against concentration. Mean slopes and SEMs (μv) against concentration (ED_{50} units). An ED_{50} unit is equivalent to end-tidal concentrations of enflurane 1.68%, halothane 0.75% and isoflurane 1.15%. Mean slopes that are significantly different from zero (SEM of individual agent was used to test this) are indicated by * = $P<0.05$. The pooled estimate of the between patient S.D. of the variable, derived from an analysis of variance, was used to test for differences between anaesthetics. The only significant difference at $P<0.05$ was between the effects of halothane and enflurane on V amplitude ($P<0.001$).

	Amplitudes	
	Mean (SEM) slope (μv ED_{50} units^{-1})	
	III	V
halothane (n = 6)	-0.01 (0.026)	0.03 (0.038)
enflurane (n = 6)	-0.02 (0.028)	-0.13* (0.039)
isoflurane (n = 6)	-0.02 (0.013)	-0.05* (0.013)
pooled estimate of S.D.	0.057	0.079

Comparisons between drugs: The mean slopes against concentration in ED_{50} units in table 8.3., showed no significant differences for latencies and interpeak intervals between the three inhalation agents. Fig.8.8. illustrates that the means slopes for halothane and enflurane were not significantly different when expressed in the units of equipotency. The slopes were 0.27 and 0.38 ms ED50 $units^{-1}$ for enflurane and halothane respectively. Enflurane produced a significantly greater decrease in V amplitude (Table 8.4.) compared to halothane.

8.3. *Early cortical response*

8.3.1. *Description of changes*

Effect of thiopentone induction: Using averages of small numbers of stimuli, the effect of thiopentone induction on the early cortical response is demonstrated in Fig.8.9. Waves Pa, Nb, and Pb (P1) were depressed following the injection and within 6-8 minutes the response recovers to a 'three wave' AER pattern. In this particular patient the early cortical response appeared to have completely recovered by the time the first datum point (at zero time or zero concentration) was sampled. In some patients however there may have been a slight carry-over effect resulting in the initial amplitudes of waves Pa and Nb being slightly reduced or the latencies slightly extended. This carry-over effect would diminish as the study progressed.

Effects of general anaesthetics: All six general anaesthetics produced marked changes in the early cortical waves compared to the saline control group. The latencies of Pa and Nb were prolonged and their amplitudes were reduced with increasing concentrations of all six drugs. Examples are shown in Fig.8.10. In the patients given halothane and Althesin the latencies of Pa and Nb increased and their amplitudes reduced. No such changes were seen in the case of the patients given the saline infusion. In the latter case throughout the study the AERs resembled the post-induction AER.

Irrespective of which anaesthetic produced these changes, they were reversed when it was discontinued. This is well shown in Fig.8.11. In this patient, ten minutes after the etomidate infusion was turned off, by which time the serum etomidate level

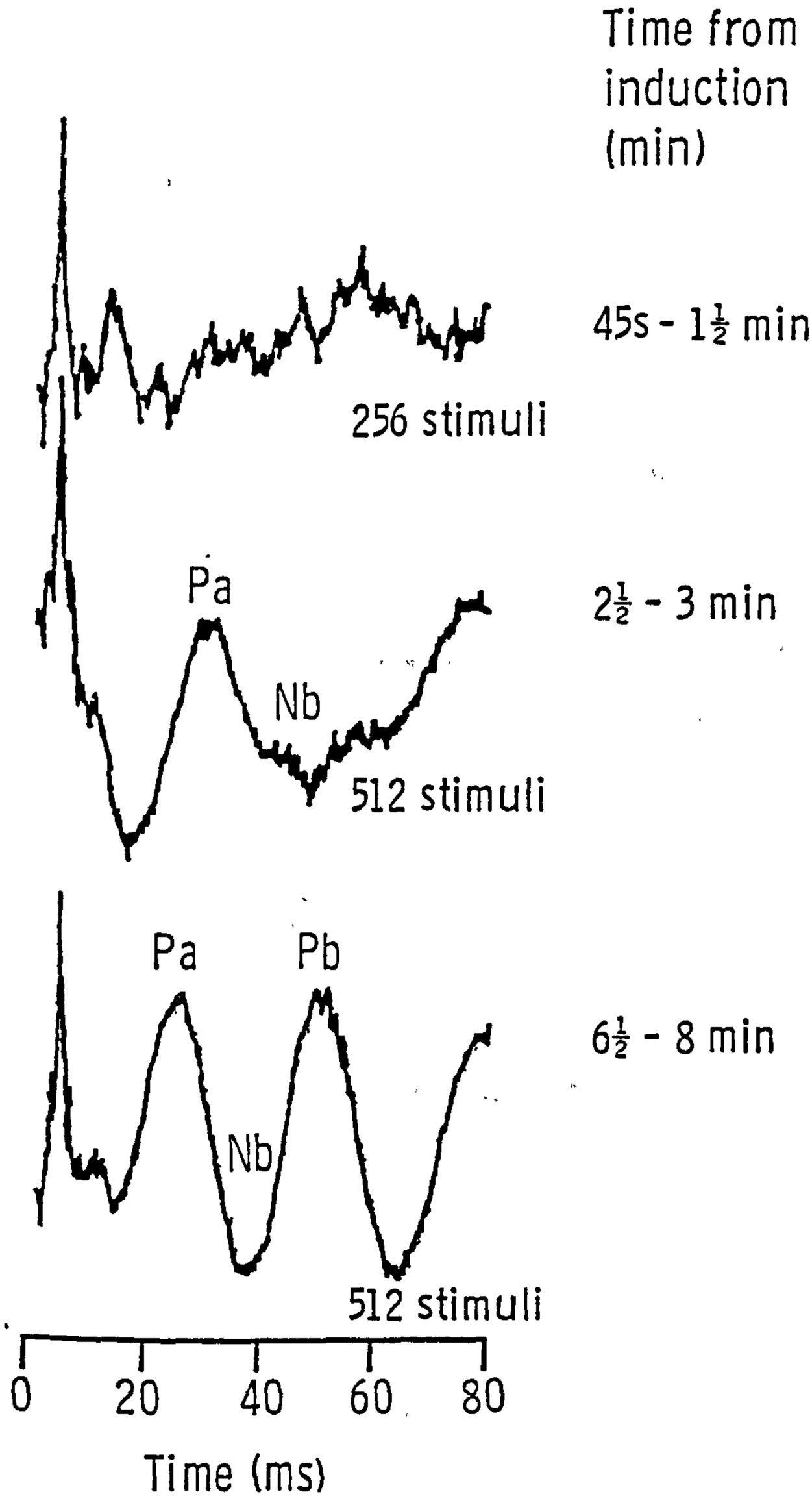
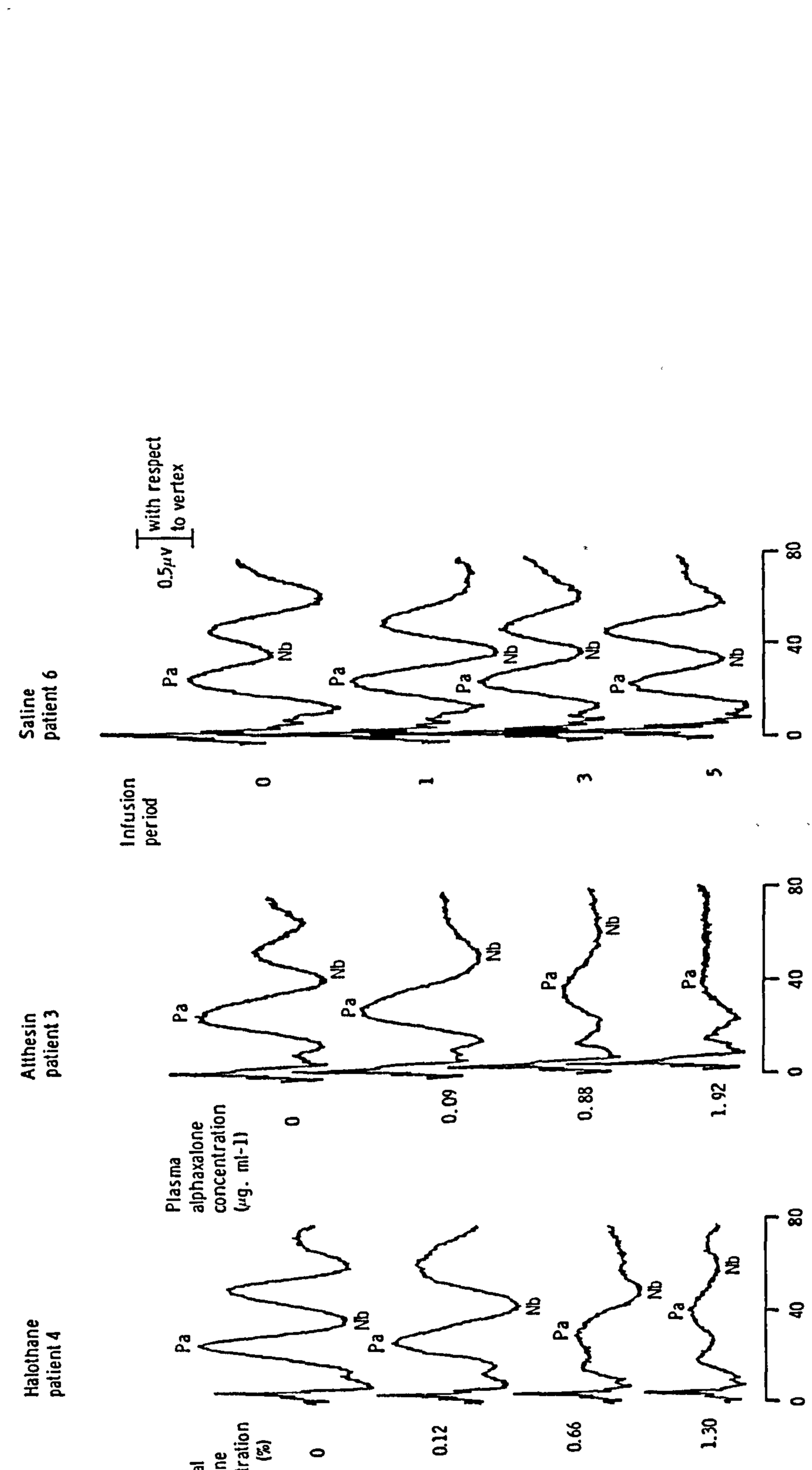


Fig.8.9. Changes in the early cortical response at intervals following thiopentone induction (EEG changes in Fig.8.2.).



Early cortical responses in patients who received a) halothane or b) Althesin or c) saline infusions. At the end of each infusion period labelled zero anaesthesia was maintained on 70% nitrous oxide, 30% oxygen.

Fig.8.10.

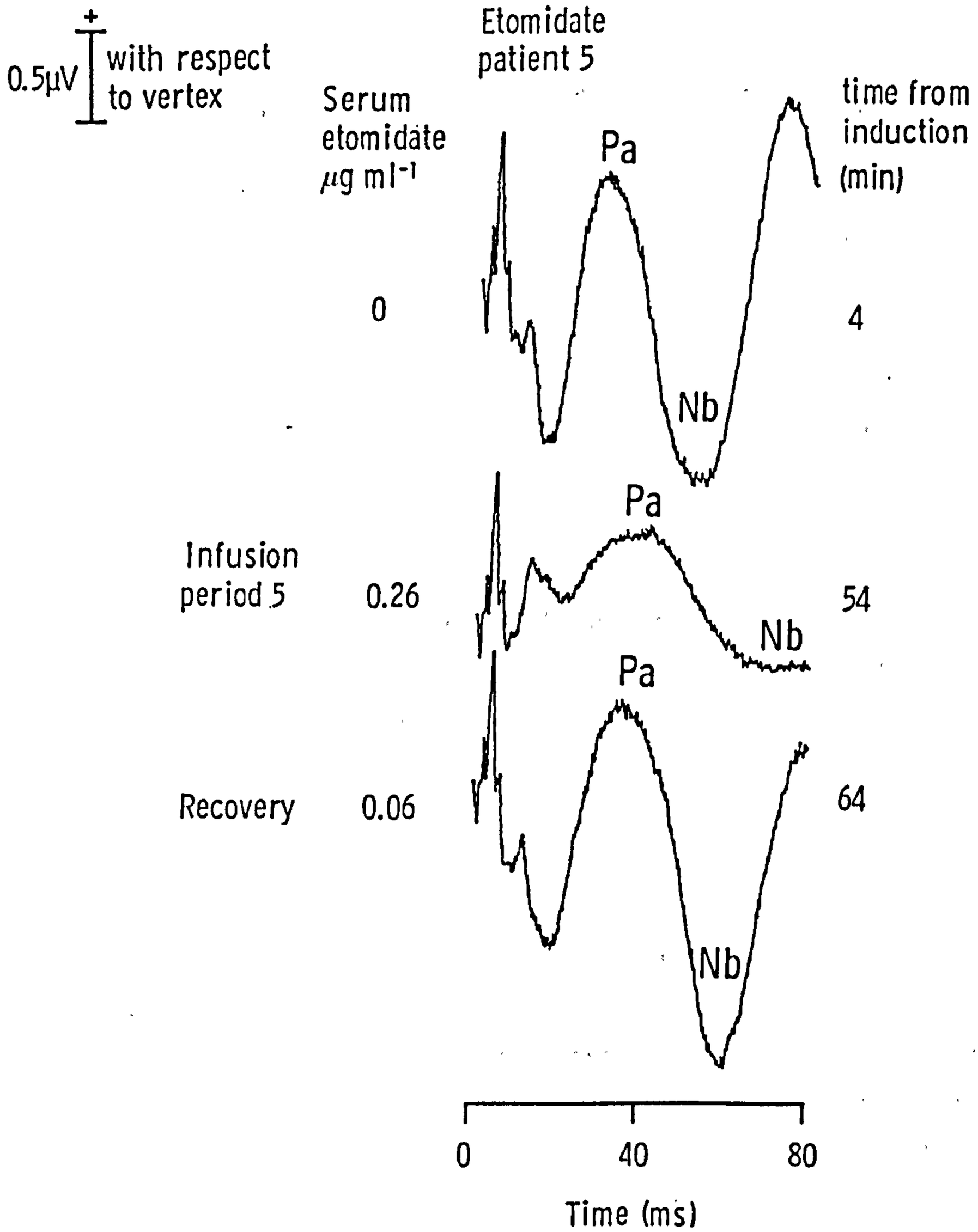


Fig.8.11. Early cortical responses in a patient in whom recovery from etomidate was monitored. The etomidate infusion was discontinued and the patient remained on 70% nitrous oxide, 30% oxygen. (Taken from Thornton et al. 1985, British Journal of Anaesthesia.)

had fallen to 0.06 μg ml^{-1}, the final AER was recorded. It was very similar in appearance to the AER which had been recorded before the etomidate was added, 60 minutes previously. This is evidence that the changes observed with the general anaesthetics are not simply time related changes but result from changes in concentration. Fig.8.12. gives further support for this. In this patient the Pa/Nb complex was severely depressed in the first infusion period when, as a result of a technical problem, a bolus of Althesin was given. The infusion rates were corrected but the outcome was that plasma alphaxalone levels rose abruptly and remained high throughout. The Pa/Nb complex remained depressed such that there was no difference between the AERs at 14 and 64 minutes. (The data of this patient were omitted from the statistical analyses).

8.3.2. *Statistical analyses - details in 7.5.*

Comparisons of general anaesthetics with saline: Using the data of all the patients confirmed that there were effects of all six general anaesthetics on the early cortical variables. These were real effects and not simply time-related trends.

Log_e of the early cortical latencies and amplitudes were plotted against time. (Other transformations were tried, such as the exponential of the latencies or amplitudes, log_e of time, or concentration, and combinations of these. However, log_e of the dependent variable gave the best improvement in linearity and has therefore been used throughout the thesis. In the tables and figures the data have been transformed back to the original units. Proportional changes and 95% confidence intervals are given instead of means and SEMs). To illustrate the variability between patients, the slopes for all six drugs and saline are shown in Fig.8.13. (Each datum point represents one patient given one drug or saline). The mean slope against time for each drug and saline are given in Table 8.5. The mean slopes of Pa and Nb latency and amplitude were significantly different from the saline group in all cases except for the reduction in Nb amplitude by halothane (P=0.12).

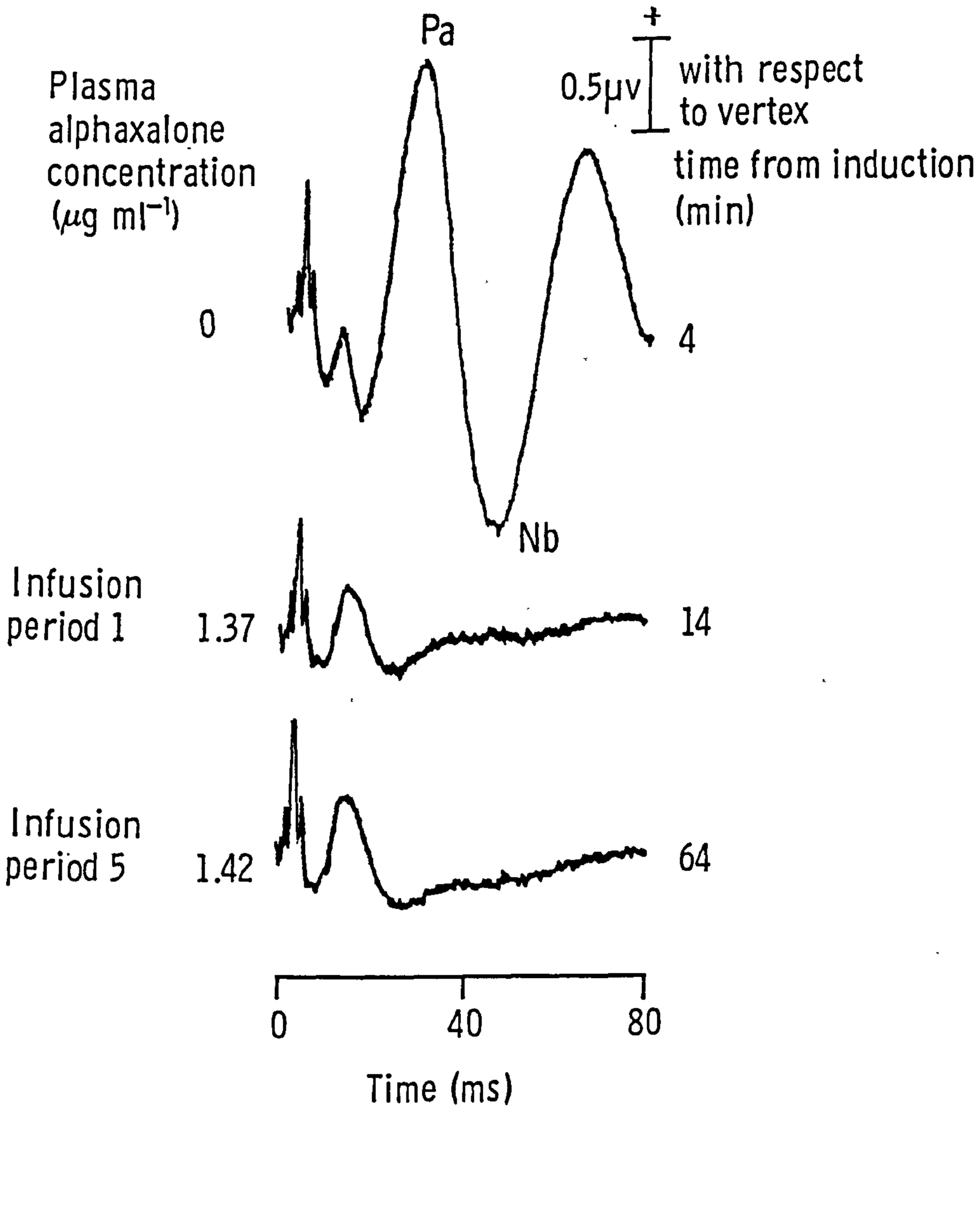


Fig.8.12. Early cortical responses in a patient following induction of anaesthesia and at two similar blood levels of alphaxalone 14 and 64 minutes later. (Taken from Thornton et al. 1986, British Journal of Anaesthesia.)

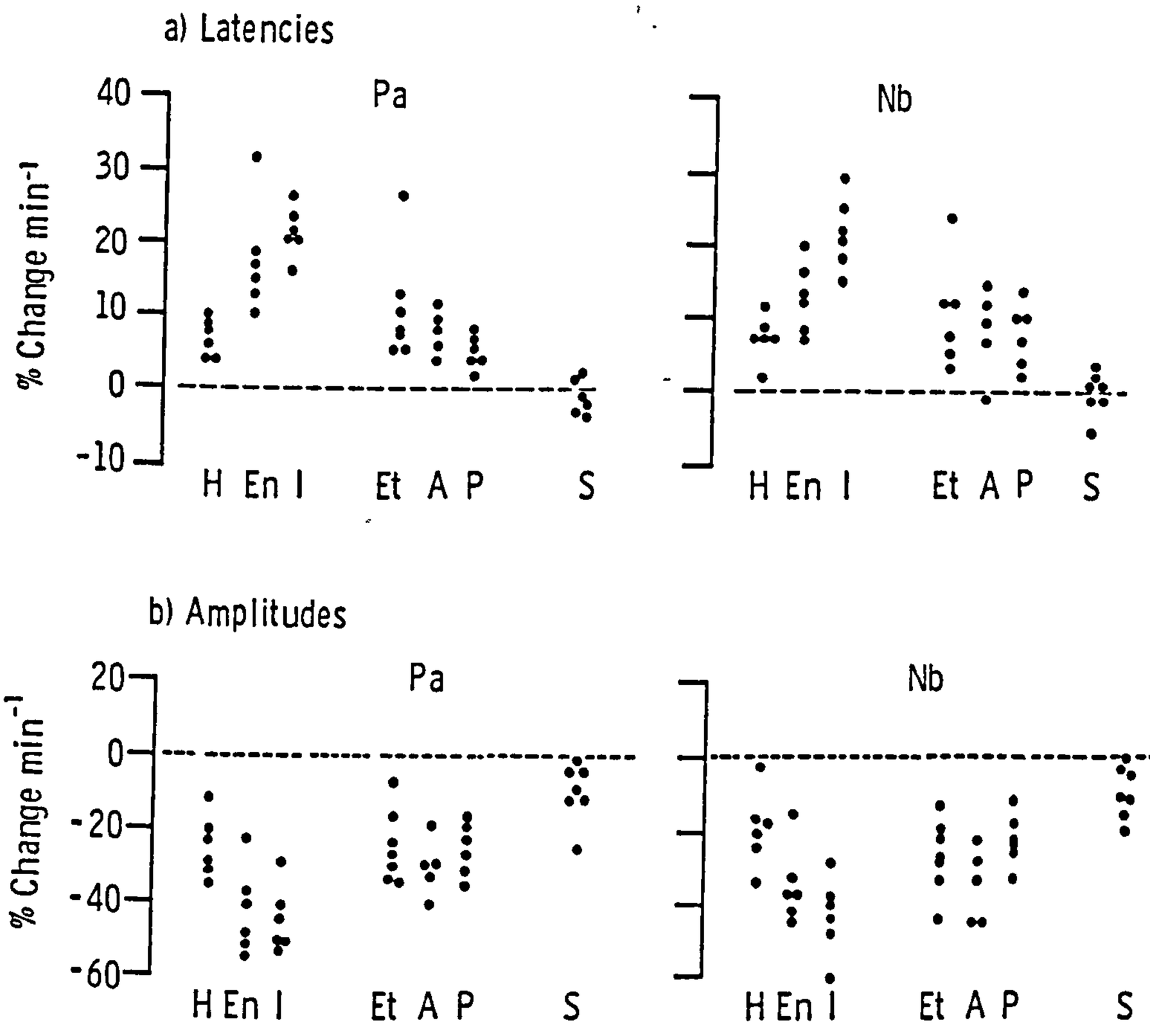


Fig.8.13. Slopes (% change) against time (min) of early cortical waves Pa and Nb a) latencies and b) amplitudes for individual patients. Each patient received one of the six general anaesthetics or saline (H=halothane, En=enflurane, I=isoflurane, Et=etomidate, A=Althesin, P=propofol and S=saline).

Table 8.5. Early cortical latencies and amplitudes - regressions against time. Mean slopes and 95% confidence intervals (% change) against time (min). Mean slopes that are significantly different from that of saline are indicated by * = P<0.05, ** = P<0.01, *** = P<0.001. The pooled estimate of the between patient S.D. of the variable, derived from an analysis of variance, was used to test for differences between anaesthetic agents and saline.

		Latencies				Amplitudes			
		Mean slopes and 95% confidence intervals				(% change min^{-1})			
		Pa		Nb		Pa		Nb	
halothane	(n = 6)	7**	(4 to 11)	8*	(4 to 13)	-25*	(-16 to -33)	-20	(-10 to -29)
enflurane	(n = 6)	18***	(14 to 22)	14**	(9 to 19)	-43***	(-37 to -49)	-36***	(-28 to -43)
isoflurane	(n = 6)	20***	(16 to 23)	23***	(18 to 28)	-47***	(-40 to -52)	-45***	(-38 to -51)
etomidate	(n = 7)	10***	(7 to 14)	10***	(6 to 15)	-25**	(-17 to -32)	-27**	(-19 to -35)
Althesin	(n = 5)	8**	(4 to 12)	9**	(4 to 14)	-31**	(-22 to -39)	-36***	(-27 to -44)
propofol	(n = 6)	6*	(2 to 9)	9**	(5 to 14)	-26*	(-17 to -33)	-22*	(-13 to -31)
saline	(n = 7)	1	(-4 to 3)	0	(-4 to 3)	-9	(1 to -18)	-9	(1 to -19)

Table 8.6. Early cortical latencies and amplitudes - regressions against concentration. Mean slopes and 95% confidence intervals (% change) against concentration (ED_{50} units). An ED_{50} unit is equivalent to end-tidal concentrations of enflurane 1.68%, halothane 0.75% and isoflurane 1.15%, blood propofol 9.76 μg ml^{-1}, plasma alphaxalone 11.23 μg ml^{-1} and serum etomidate 2.35 μg ml^{-1}. Mean slopes that are significantly different from zero (SEM for individual anaesthetic agents were used to test this) are indicated by * = P<0.05, ** = P<0.01 and *** = P<0.001. The pooled estimate of the between patient S.D. of the variable, was derived from an analysis of variance, and used to test for differences between the inhalation agents (see text).

		Latencies Mean slopes and 95% confidence intervals		Amplitudes (% change ED_{50} units $^{-1}$)	
		Pa	Nb	Pa	Nb
halothane	(n = 6)	24*** (16 to 33)	29** (14 to 45)	-59** (-41 to -71)	-48** (-25 to -65)
enflurane	(n = 6)	62** (32 to 100)	45** (26 to 68)	-81*** (-63 to -90)	-73** (-55 to -84)
isoflurane	(n = 6)	58*** (35 to 85)	60** (34 to 92)	-76*** (-63 to -85)	-74** (-57 to -84)
etomidate	(n = 7)	387***(110 to 1028)	402* (64 to 1433)	-98*** (-94 to -99)	-99** (-89 to -100)
Althesin	(n = 5)	560***(264 to 1096)	896 (-16 to 7469)	-100***(-100 to -100)	-100** (-99 to -100)
propofol	(n = 6)	80** (39 to 133)	139** (40 to 307)	96** (-85 to -99)	-94** (-79 to -99)

Dose relationships: For all six anaesthetics the changes in the early cortical variables (log_e transformed) were linearly related either to end- tidal or blood concentration. A typical example is given in Fig.8.14. where Pa amplitude is plotted against blood propofol concentration in μg ml^{-1} and ED_{50} units for the six patients who received propofol infusions. The mean slopes against concentration, in ED_{50} units, for each drug for all the early cortical variables are given in Table 8.6. In all cases, except for the effect of Althesin on Nb latency, the mean slopes of the latencies significantly increased and the amplitudes significantly decreased compared to zero.

Comparisons between drugs: On the basis of the derived ED_{50} estimates an attempt was made to compare the effect of the six general anaesthetics on the early cortical variables.

First the mean slopes against concentration of the inhalation agents in ED_{50} units were compared. Halothane was significantly less potent than the other two drugs in its effects on Pa and Nb latency and amplitude. For Pa latency and Nb amplitude halothane was significantly different from enflurane ($P<0.01$, $P<0.05$) and isoflurane ($P<0.05$); for Nb latency it was significantly different from isoflurane ($P<0.05$) and for Pa amplitude it was significantly different from enflurane ($P<0.05$). Isoflurane and enflurane did not differ significantly in their effects on these variables.

Secondly an attempt was made to compare the effects of the inhalation and intravenous agents on the early cortical variables. However the differences between the slopes of the inhalation and intravenous agents in table 8.6. are extremely large and it is not statistically valid to compare a mean of 29%, confidence interval 14 to 45% with a mean of 896%, confidence interval -16 to 7469%. These quantitative comparisons were therefore not pursued. The problem of estimating equipotency is discussed in 12.2.3.

8.4. *Arterial pressure and Deep body temperature*

The mean changes in arterial pressure throughout the study period for the different anaesthetic agents are is given in table 8.7.

With the exception of etomidate all anaesthetics produced significant depression of the arterial pressure (see 7.5.1. for details of statistical test), however, in no patient did it decrease below 80 mmHg systolic.

Table 8.7. Changes in systolic arterial pressure with the various test agents. The mean change, SEM and the significance of the difference from zero at P<0.05), over the period of administration of the test agent or saline are given.

	Systolic arterial pressure (mmHg)		
	Mean	SEM	significance
halothane (n = 6)	-28	5	<0.01
enflurane (n = 6)	-28	3	<0.001
isoflurane (n = 6)	-27	7	<0.05
etomidate (n = 7)	-10	5	ns
Althesin (n = 5)	-19	3	<0.01
propofol (n = 6)	-38	7	<0.01
saline (n = 7)	3	3	ns

There were small decreases in deep body temperature in some patients although these never exceeded 0.5 °C over the duration of the study.

CHAPTER 9

EFFECT OF SURGICAL STIMULATION ON THE AER

9.1. *Introduction*

To measure 'depth of anaesthesia' the changes in the AER must reflect the balance between depression of the CNS due to anaesthetic drugs and stimulation by sensory events such as surgery. Otherwise they are simply sophisticated bioassays of anaesthetic concentration. Chapter 8 reported changes in the AER due to general anaesthetics in patients without surgical stimulation. This chapter reports the effect of surgical stimulation (patient details Table 9.1.) on the AER with the anaesthetic concentration maintained constant (details of protocol in 5.4.).

Table 9.1. Patient information for the surgery study. Age and operations of the patients (all female) who took part in the study.

Patient	Age (yr)	Operation
1	41	Total abdominal hysterectomy
2	36	Bilateral varicose veins strip
3	38	Total abdominal hysterectomy
4	26	Left ankle triple arthrodesis
5	34	Right big toe arthrodesis
6	44	Total abdominal hysterectomy
7	36	Total abdominal hysterectomy
8	50	Total abdominal hysterectomy
9	37	Tubal surgery
10	47	Total abdominal hysterectomy
11	35	Total abdominal hysterectomy

9.2. *Effect of surgery*

9.2.1 *Description of data*

The early cortical traces of an anaesthetised patient before and during surgical stimulation are shown in Fig.9.1. The most striking changes were in the amplitudes of Pa, Nb and Pb/Pc which were larger during surgery compared to before, resembling what would be expected from a lower end-tidal halothane concentration. For instance, the AER of the patient shown in Fig.9.1. was in appearance midway between those at 0.12% and 0.66% end-tidal halothane in Fig.8.10. whereas before surgery it was closer to the 0.12% AER. In this patient the changes in the AER were associated with increased frequency and diminished amplitude in the EEG (Fig.9.2.). Not all patients showed these AER changes. Pa showed an overall increase following incision in 6 out of 11 patients, Nb in 8 out of 11 and Pb/Pc in 9 out of 11 patients. The Nb and Pb/Pc amplitude data for individual patients are plotted in Fig.9.3.

9.2.2. *Statistical Analyses*

The increased amplitudes of waves Nb and Pb/Pc during surgery compared to before were statistically significant (details of statistical tests used in 7.5.2.) as were the increased latencies of V and the III-V interval (mean changes given in Table 9.2.).

Table 9.2. Mean changes following surgery, for the eleven patients, for AER latencies and amplitudes.

		Difference (during - before surgery)		
		D	SEM or 95% c.i.	significance
Latency (ms)	I	0.01	0.019	ns
	III	0.02	0.017	ns
	V	0.07	0.016	<0.01
	III-V	0.04	0.015	<0.05
(% change)	Pa	2	-2 to 7	ns
	Nb	4	-3 to 12	ns
	Pb/Pc	5	-1 to 12	ns
Amplitude (% change)	Pa	13	-13 to 46	ns
	Nb	14	1 to 29	<0.05
	Pb/Pc	17	4 to 31	<0.01

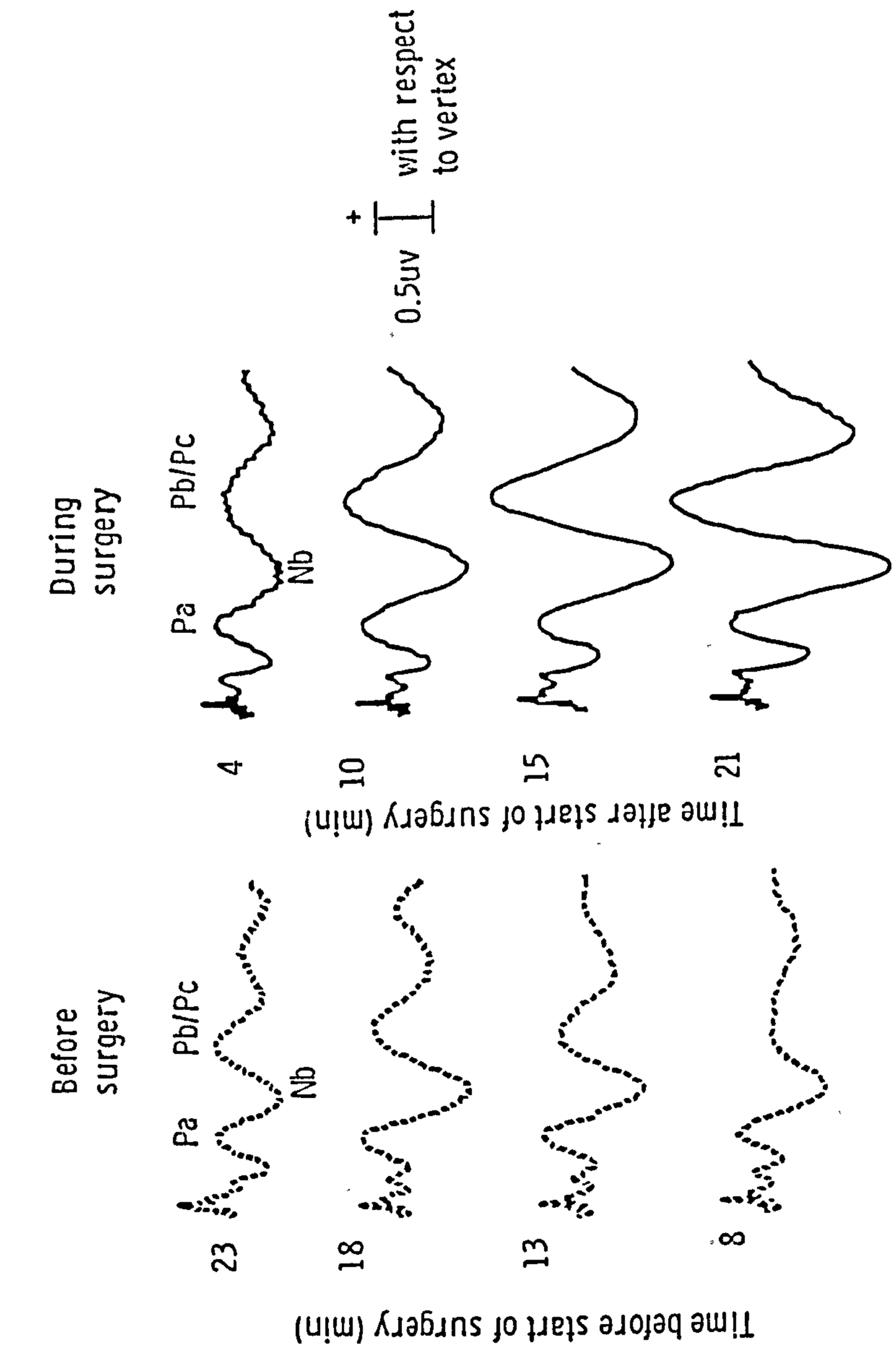


Fig.9.1. The early cortical responses of one patient a) before and b) during surgery starting from first incision. Each average AER took approximately six minutes to collect. The times given correspond to the middle of that period. (Taken from Thornton et al. 1988, British Journal of Anaesthesia.)

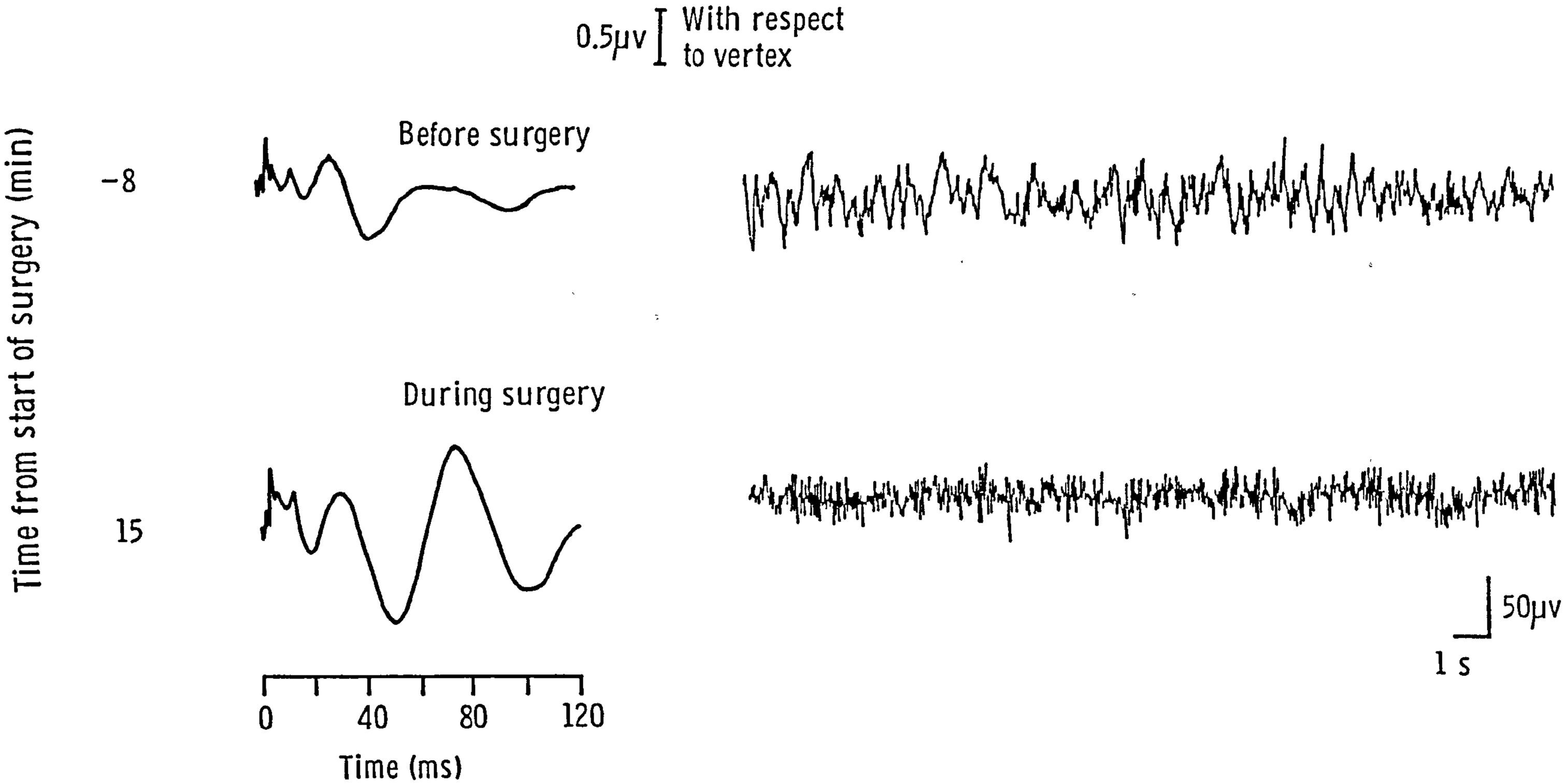


Fig.9.2. The effect of surgical stimulation on a) the early cortical response b) the EEG. Each average AER took approximately six minutes to collect. The times given correspond to the middle of that period.

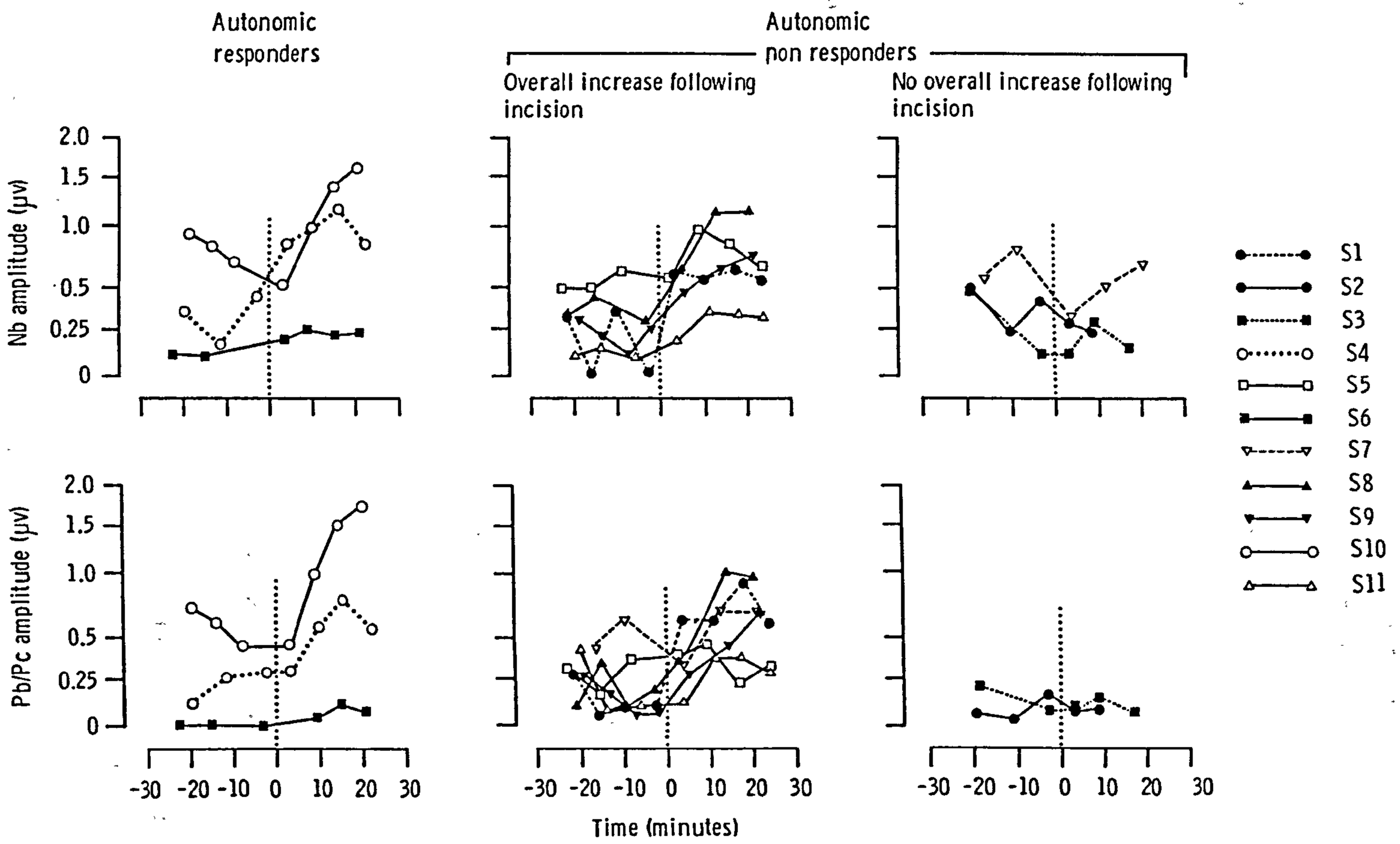


Fig.9.3. Nb and Pb/Pc amplitudes plotted against time (min) for individual patients. Incision is indicated by a vertical dotted line. For definition of autonomic 'responder' and 'non-responder' see text.

However, only the amplitudes of Nb and Pb/Pc were specifically affected by surgical stimulation as only these variables showed significant surgery X period interactions. To test for a significant surgery X period interaction the trends before and during surgery were derived from two consecutive 12 minute periods. The means for each of these period are presented in Table 9.3.

Table 9.3. Trends, before and during surgery, in AER latencies and amplitudes. Mean of the 11 patients,for consecutive 12 minute periods, before and during surgery, and significance of the surgery X period interaction.

			Before incision		After incision		
			24-12 min	12-0 min	0-12 min	12-24 min	
Latency	(ms)	I	1.87	1.87	1.89	1.89	ns
		III	4.12	4.11	4.14	4.14	ns
		V	6.15	6.18	6.23	6.24	ns
		III-V	2.03	2.07	2.09	2.10	ns
		Pa	34.1	34.3	35.0	35.1	ns
		Nb	51.2	52.7	53.6	54.7	ns
		Pb/Pc	71.8	72.7	76.3	75.6	ns
Amplitude	(μv)	Pa	0.43	0.39	0.44	0.49	ns
		Nb	0.37	0.32	0.46	0.61	<0.01
		Pb/Pc	0.21	0.22	0.32	0.53	<0.01

These period means are plotted for Pa, Nb and Pb/Pc amplitudes in Fig.9.4. Following the start of surgery there was a statistically significant change in the trend. During surgery the means were higher in the second period compared to the first whereas before surgery there was essentially no difference between the two periods. No such changes in trend were seen and the surgery X period interaction were not significant in the case of the brainstem latencies suggesting that the observed changes in these variables were gradual increases over the period of the study which would have occurred even had there been no surgery.

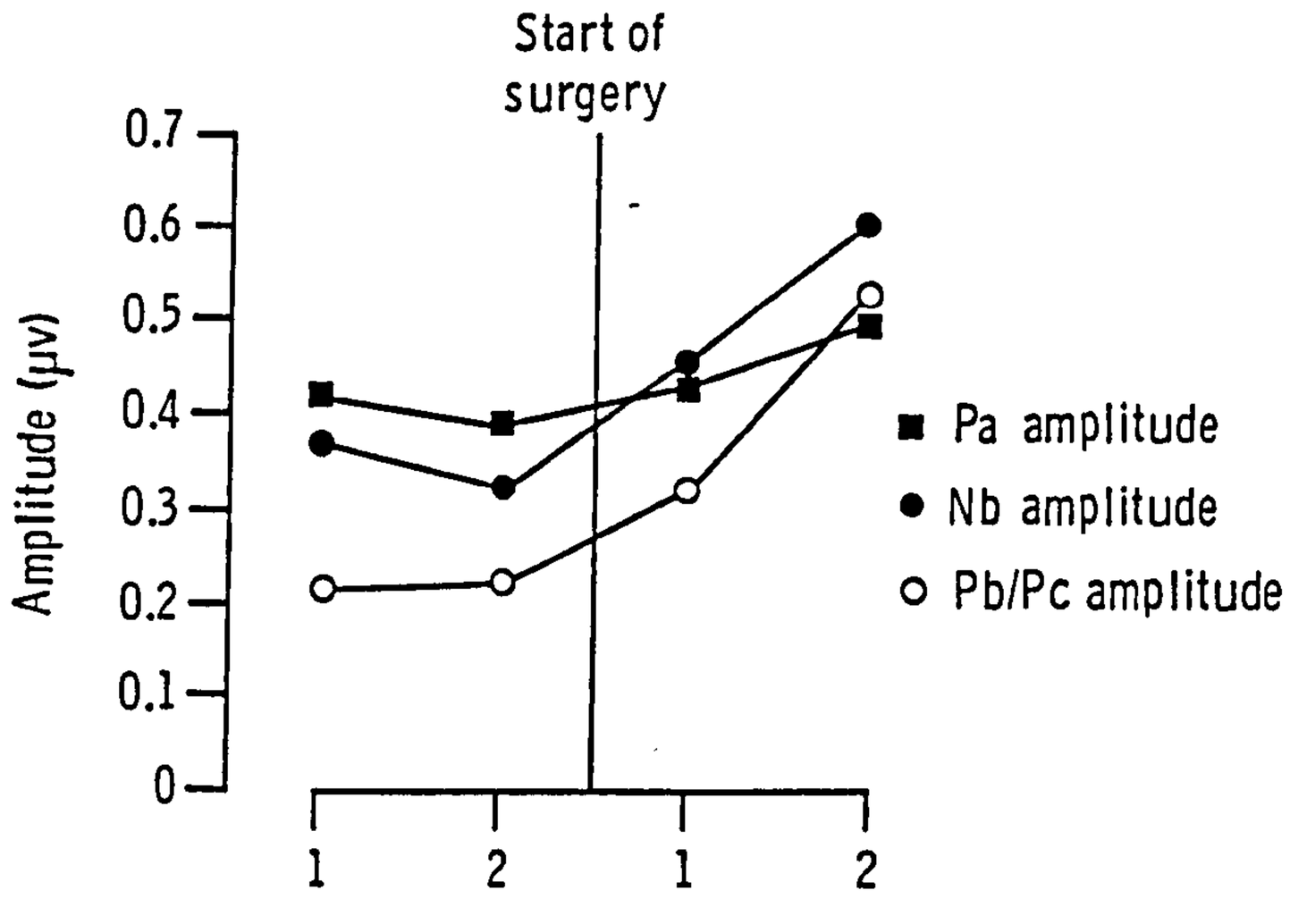


Fig.9.4. Means for the eleven patients, of Pa, Nb and Pb/Pc amplitude for the periods 1 (24-12 min) and 2 (12-0 min) before incision, and periods 3 (0-12 min) and 4 (12-24 min) after incision.

9.3. *Autonomic responders versus non-responders*

9.3.1. *Description of data*

Only three of the eleven patients showed a clear response to surgery as judged by autonomic signs. These patients' data are shown in Fig.9.3. (far left). These three patients all showed increases in the amplitudes of Nb and Pb/Pc. It was the possibility of a relationship between the autonomic changes and the changes in the AER that prompted the inclusion of the autonomic "responder" and "non-responder" classification in the analysis of variance model. Table 9.4. summarises the autonomic changes on which this classification was based along with the anaesthetists overall impression at the time.

Table 9.4. Autonomic responses to surgical stimulation of the 11 patients who took part in the study. a) Pupillary dilatation; ++ sustained for longer than 1 hr; ++ for longer than 10 mins; + some evidence; - no evidence. b) Mean increase in BP; +++ in excess of 20 mmHg; ++ in excess of 10 mmHg; + increase 0-10 mm Hg; - no change or a decrease. c) Mean increase in Heart Rate; ++ in excess of 10 min^{-1}; + some increase; - no change or a decrease. d) Sweating; + evidence - no evidence. e) Tears; + some evidence; - no evidence. f) Overall clinical impression ; ++ unambiguous; + equivocal autonomic response to surgery; - no response.

Patient	(a) Pupillary Dilatation	(b) Mean Inc. B.P.	(c) Mean Inc. H.R.	(d) Sweating	(e) Tears	(f) Clinical impression
1	+	-	-	-	-	-
2	-	-	-	-	-	-
3	-	++	-	-	-	-
4	++	+++	++	-	-	++
5	-	-	-	-	-	-
6	+++	++	-	-	-	++
7	+	++	-	-	+	+
8	+	+	-	-	-	+
9	-	++	-	-	-	-
10	+++	++	-	-	+	++
11	+	-	-	-	-	-

The three patients who were classed as unambiguous responders had high scores for pupillary dilatation and for the mean increase in blood pressure. None of the patients showed sufficient change in autonomic function to prompt the anaesthetist to administer more general anaesthetic agent and no patient reported awareness of the surgical procedure, hearing voices or unusual dreams.

9.3.2. *Statistical analyses*

None of the variables tested showed a significant surgery X responder interaction (see 7.5.2. for statistical tests used), that is the effects of surgery on the AER were not different in the three patients classified autonomic "responders" to those considered to be "non or equivocal responders". There is however little statistical power for this comparison.

CHAPTER 10

AN AER INDICATOR OF 'AWARENESS'

10.1. *Introduction*

In this chapter the AER is examined for changes which indicate whether a paralysed patient is awake or anaesthetised. This is particularly relevant to surgical operations such as Caesarian sections where there is a delicate balance between the dose of anaesthetic required to anaesthetise the mother and that which has adverse effects on the infant.

The hypothesis was tested that a reliable marker of awareness could be found in the initial changes of the early cortical AER. In particular that the 'three wave' pattern in Fig.10.1a) is consistent with 'awareness' (a concept discussed at length in Chapter 12) and that this changes to the 'two wave'pattern in b) when a small amount of halothane is added and the patient becomes unconscious.

This hypothesis was based on a number of observations:-

1) The 'three wave' AER pattern is frequently seen in the period immediately following tracheal intubation, a period which is associated with a high risk of awareness.

2) The 'three wave' pattern changes to a 'two wave' pattern with a change from awake to asleep. Erwin and Buchwald (1986b), whose work is discussed in 4.3.3. showed that the central wave Pb (P1) in Fig.10.1.a) was present when the subject was awake but was attenuated or disappeared completely during stage 2 sleep. It appeared again during rapid-eye- movement (REM) sleep suggesting a generator system for this wave which is functionally related to arousal.

3) The change from the 'two wave ' to 'three wave' AER in a patient in the saline control group (Chapter 8) was associated with signs

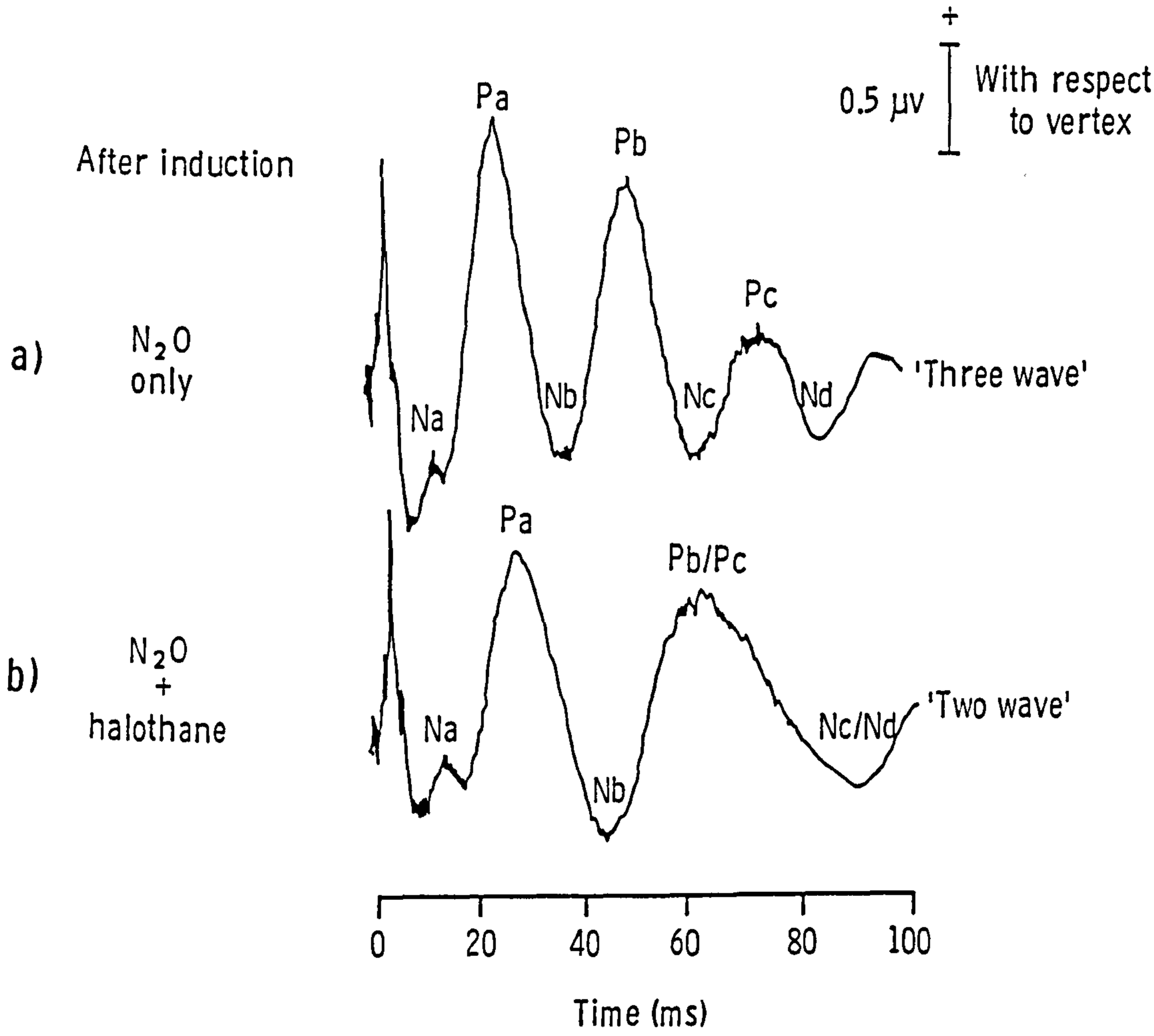


Fig.10.1. Early cortical response in a patient following induction of anaesthesia and tracheal intubation. In a) there were three positive waves Pa, Pb and Pc between the latencies 15-100 ms. At this time anaesthesia was maintained on 70% nitrous oxide, 30% oxygen. In b) following the addition of halothane to give an end-tidal of 0.12% these were replaced by two positive waves Pa and Pb/Pc.

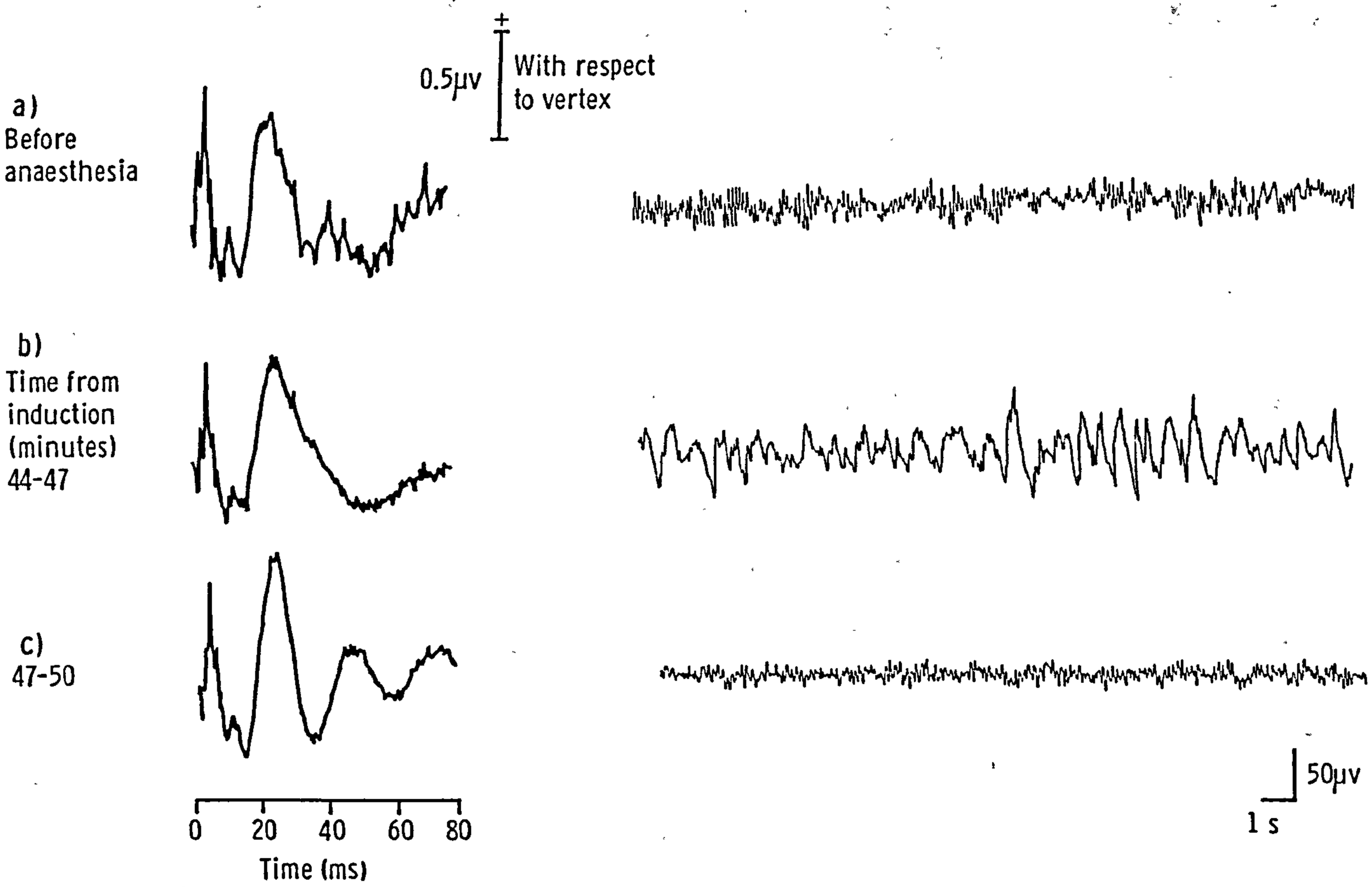


Fig.10.2. Early cortical responses and EEGs in a patient receiving a saline infusion, with anaesthesia maintained on 70 %nitrous oxide, 30% oxygen. At 47 minutes there was an abrupt change in the EEG from an 'asleep' to an 'awake' pattern.

of arousal in the EEG. In this patient, whose data are shown in Fig.10.2., following induction with thiopentone, anaesthesia was maintained on 70% nitrous oxide 30% oxygen (see 5.3 for detailed protocol). After 47 minutes of an EEG normally associated with sleep, shown in Fig.10.2.b), this pattern changed to one that was associated with wakefulness, shown in Fig.10.2.c). (EEG changes during wakefulness and sleep are described in 4.3.3.) Concurrent with this abrupt change in the EEG was a change in the AER from the 'two wave' pattern shown in Fig.10.2.b) to the 'three wave' pattern in Fig.10.2.c).

As a first stage in testing the hypothesis a discriminant function analysis was carried out (details in 7.5.3.) to extract reliable mathematical criteria which distinguished the 'three' from the 'two wave' AER pattern. (Counting the number of waves was not reliable as it was sometimes difficult to be sure whether a third wave was present.) The zero and low concentration data from Chapter 8 were used for this purpose. Then in further clinical studies, presented in this chapter, evidence was obtained for the association of the criteria chosen, with the awake and anaesthetised states respectively.

10.2. *Extraction of mathematical criteria to distinguish 'three and two' wave AERs*

The experimenter categorised 36 pairs of AERs into 'three wave' or 'two wave' patterns. The most common transition was that shown in Fig.10.1. namely, a 'three wave' pattern following induction of anaesthesia to 'two wave' following addition of a low concentration of the test agent. The number of patients showing this transition, are given in column 1 of Table 10.1.. Other types of transition are shown in columns 2, 3, 4 and 5. The data from the patients in column 1 were used to derive mathematical criteria to distinguish 'three and two wave' AER patterns. From the five latencies, Na, Pa, Nb, Pb (or Pb/Pc) and Nc (or Nc/Nd) entered into the discriminant analysis program the single variable which gave closest agreement with the experimenter's 'three/two' wave classification was Nb latency. The pair of variables which, in combination, gave closest agreement were Pa and Nb latency. Using three or more variables did not improve the agreement.

Table 10.1. Changes in AER pattern following induction of anaesthesia and the addition of low concentrations of anaesthetic. Experimenter's categorization of 'three' wave to 'two' wave - the first number is the pattern following induction; subsequent numbers are following the addition of the test gas or the start of the infusion. The body of the table shows the number of patients for each anaesthetic drug or saline that showed that particular sequence.

	1 3 → 2	2 3 → 3 → 2	3 3 → 3 → 3	4 2 → 2	5 3 → 3
Halothane	4			1	
Enflurane	3			1	
Isoflurane	3	1		1	
Etomidate	3	1		2	1
Althesin	1			3	
Propofol	1	2		3	
Saline	1		1		3
Total	16	4	1	11	4

The criteria used to asses agreement were:-

1) The size of the residual error, when the program had subdivided the data into two populations. This should be as small as possible.

2) The number of misclassifications when the formula was tested on the data in columns 2, 3, 4 and 5 of Table 10.1.. These should be as few as possible.

The formula using Nb latency is as follows:-

$$\textit{Probability of 'three wave'} = 1 - \textit{probability of 'two wave'}$$

$$= 1/(1 + e^{f})$$

$$\textit{where } f = -108.3 + 28.5 \log_e \textit{Nb latency}$$

In Fig.10.3. this formula has been used to construct vertical lines which give the probability of a particular AER being 'three wave'. For example, the AER in Fig.10.1.a) was labelled 'three

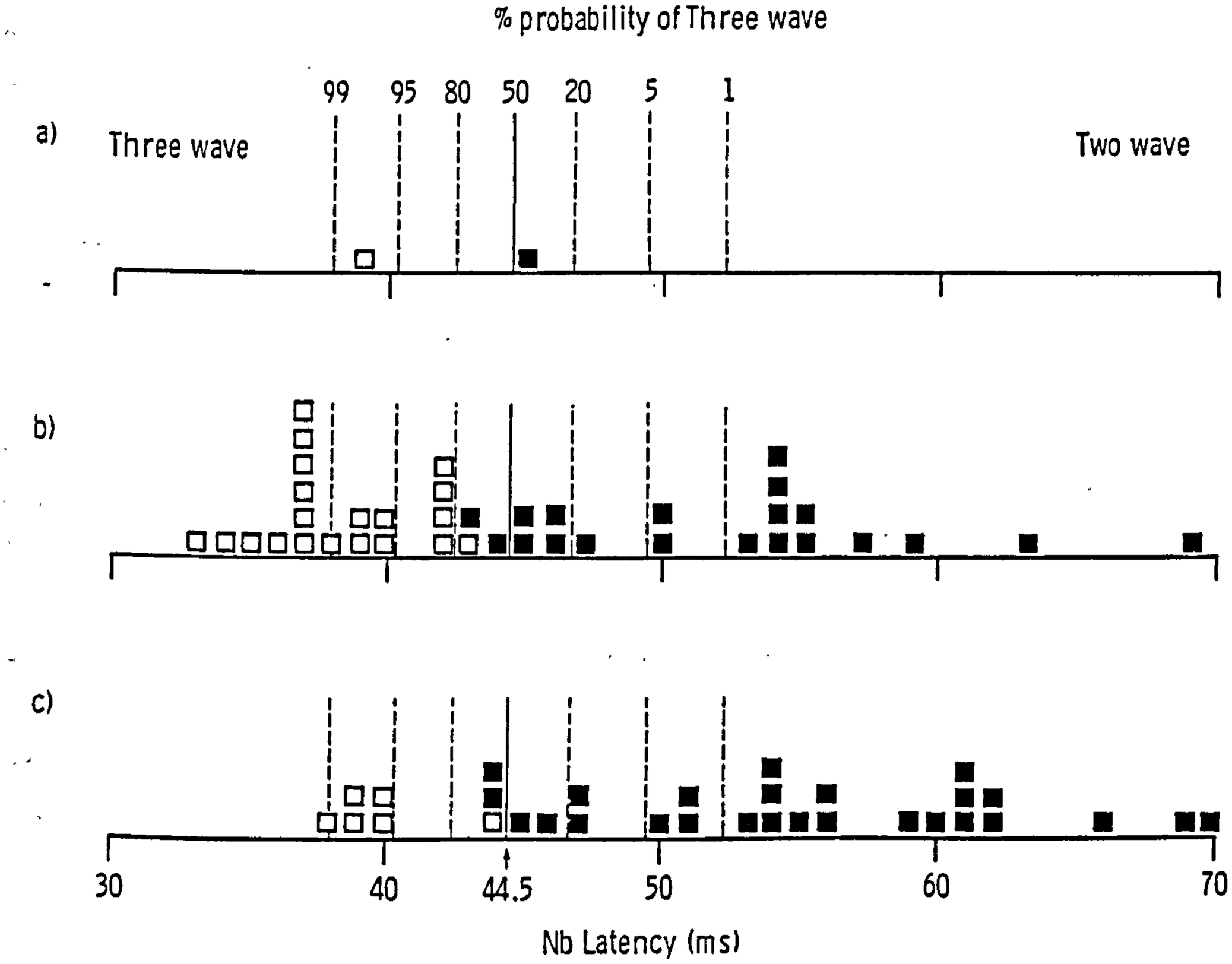


Fig. 10.3. Probability of a 'three wave' or 'two wave' AER. According to the formula, from the discriminant function analysis, the probabilities of the AER being 'three wave' are given by the vertical lines. Nb latency is plotted on the horizontal axis, each square represents one datum point. □ indicates that the experimenter classified the AER as 'three wave', ■ as 'two wave'. Data extracted from Fig.10.1. are plotted in a), data used to derive the formula in b) and data used to test the formula in c).

wave' by the experimenter. The Nb latency, which is 39 ms, when plotted (□) in Fig.10.3.a) falls midway between the 95 and 99% probability lines. From the formula therefore, this AER has a 98% chance of being 'three wave'. The AER in Fig.10.1b) was labelled 'two wave' by the experimenter. The Nb latency, which is 45 ms when plotted (■) in Fig.10.3.a) falls just to the right of the 50% probability line. From the formula therefore this AER has a 42% chance of being 'three wave' or a 58% chance of being 'two wave'.

If the 50% probability line, which corresponds to an Nb latency of 44.5 ms, is used to discriminate 'three and two wave' AERs then the classification by the experimenter and that using the formula are not in perfect agreement. This is shown in Fig.10.3b) where the data used to derive the formula are plotted. The experimenter classified two AERs as 'three wave' which the formula would classify as 'two wave'. In Fig.10.3.c) the data used to test the formula are plotted. Again, two of the AERs that the experimenter had classified as 'three wave' the formula would classify as 'two wave'. However, the agreement between the experimenter and the formula is close and the latter provides us with a simple method, based on a robust variable i.e. Nb latency, of deciding whether an AER is the 'three wave' or 'two wave pattern.

10.3. *Nb latency in relation to 'awareness'*

10.3.1. *Investigations prior to general surgery*

For the seven patients tested prior to general surgery (detailed protocol in 5.5.2.) Nb latency is plotted against time from anaesthetic induction in minutes in Fig.10.4.

Four of the patients, P1-P4, gave definite positive responses of the isolated forearm. Each gave a clear meaningful response to verbal command (•) following a period where there had been no response (o). With the addition of the inhalation agent (shaded area) the response to command disappeared. The most obvious feature of these data are that the responses to verbal command occurred when Nb latencies were equal to or less than the 44.5 ms threshold indicating that the AERs were 'three wave' and hence

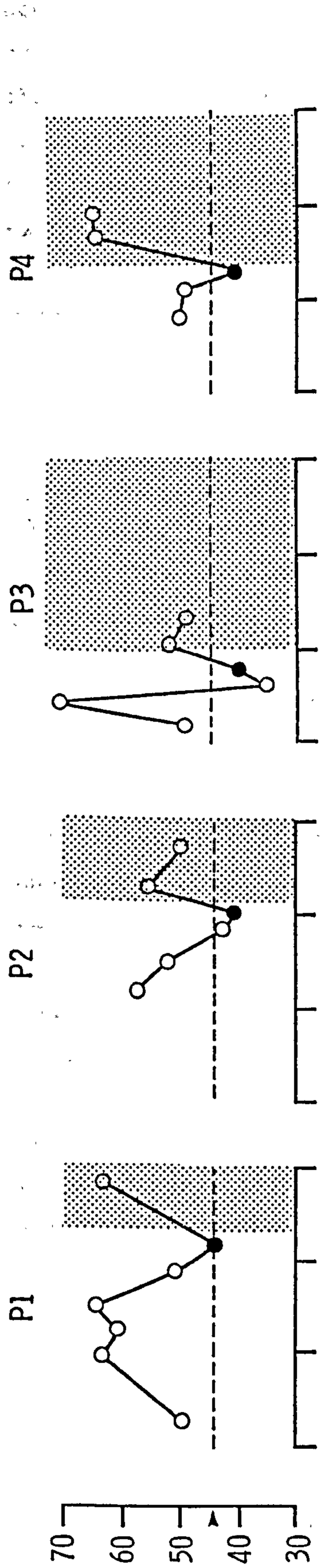


Fig.10.4. Nb latency (ms) plotted against time from induction of anaesthesia in patients prior to general surgery. Positive responses of the isolated arm to verbal command are shown as ●, a spontaneous movement by *. The nitrous oxide concentration was reduced gradually to the point where the shading indicates that an inhalation agent was administered. Nb latency of 44.5 ms is indicated by the horizontal line. (Taken from Thornton et al. 1989a, British Journal of Anaesthesia.)

according to the hypothesis 'aware'. When the inhalation agent was added the latencies increased above the threshold indicating that the AERs were 'two wave' and hence according to the hypothesis 'anaesthetised'. Most of the data of these patients were 'two wave' AERs unaccompanied by a response to verbal command. Two exceptions were patients P2 and P3 who showed 'three wave' AERs without a response to command, although a response developed within 3 minutes in each case.

In the other three patients P5-P6, there were doubts about the response of the isolated forearm. For instance, P5 developed spasms of the hand approximately 7 minutes after induction of anaesthesia (previously there was no response to command). At the time Nb latency was below the 44.5 ms threshold indicating that the AERs were 'three wave'. The hand spasms disappeared when the inhalation agent was added and Nb latency increased above 44.5 ms indicating the AER was 'two wave'.

In patients P6 and P7 the positive responses of the isolated arm to verbal command occurred shortly after induction of anaesthesia. Nb latencies in these cases were on or below the 44.5 ms threshold ('three wave'). However subsequent AERs also had latencies on or below this threshold without positive responses of the arm. The initial positive responses had disappeared but did not reappear, which is what is required for an unequivocal result. For patient P6 the short acting muscle relaxant Vecuronium had been used instead of isolating the arm with a cuff. In this patient, even after administering the inhalation agent Nb latencies did not increase above the 44.5 ms threshold. Patient P7, although he showed only one response, clinically appeared to become progressively lighter. Both arms moved at the point indicated by an asterisk and the inhalation agent was given. In retrospect, further recordings at higher concentration of inhalation agent would have been helpful in understanding the data of these two patients. It should then have been possible to observe the transition of the waveforms to the two wave pattern.

10.3.2. Investigations *during Caesarian section*

For the 8 patients undergoing elective Caesarian section (detailed protocol in 5.5.3.), Nb latency is plotted against time in

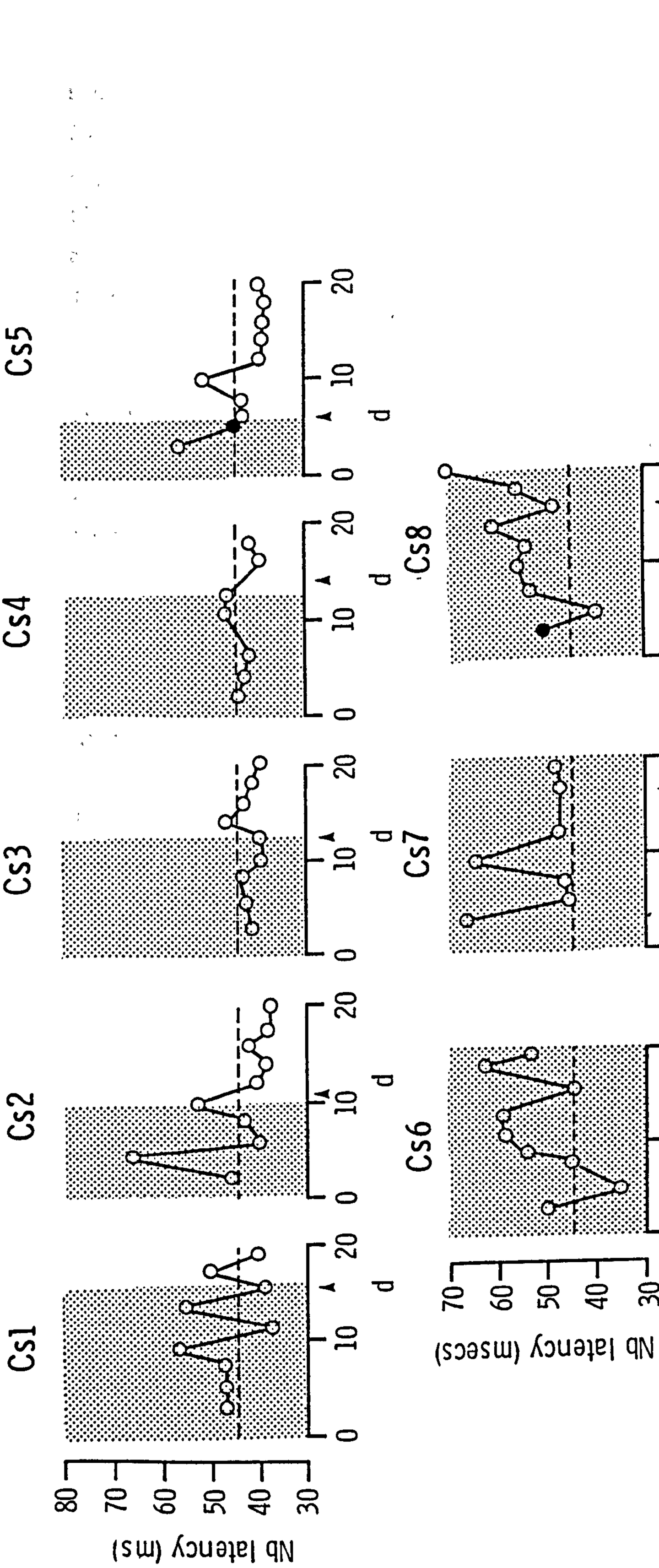


Fig.10.5. Nb latency plotted against time from induction of anaesthesia in patients undergoing Caesarian section. Positive responses of the isolated arm to verbal command are indicated by ●. Shading indicates that enflurane is being administered. In the five patients, whose data are displayed at the top of the figure, enflurane was turned off at delivery (d) and anaesthesia was maintained with nitrous oxide and oxygen supplemented with morphine. Nb latency of 44.5 ms is indicated by the horizontal line.

Fig.10.5. There were only 2 positive responses of the isolated forearm to verbal command (•) in the entire study. These were in separate patients. Nb latency was below the 44.5 ms threshold ('three wave') in one case and above ('two wave') in the other although the Nb latency in the AER epoch immediately following decreased to below the threshold.

Before delivery the latencies were distributed evenly around the threshold, however, after delivery a distinct pattern emerged. In the five patients P1-P5), in whom the enflurane was turned off at delivery the latencies were almost exclusively below the 44.5 ms threshold ('three wave') whereas in the patients P6 - P8, in whom the enflurane was continued (shaded area) the latencies were above ('two wave').

Judging by the autonomic signs, most of the patients in this group were lightly anaesthetised for most of the time. Although only 2 positive forearm responses were seen, on 14 other occasions there was movement of the arm at the time of testing. These were not associated with a particular AER pattern and may have been unrelated to the verbal commands. In several of the patients there were increases in heart rate and blood pressure as well as enlarged pupils, all of which are signs of light anaesthesia. Figs.10.6. and 10.7. show the clinical assessment of patients who were fairly representative of the group.

Patient P5 (Fig.10.6.) had raised blood pressure and spontaneous movement around induction of anaesthesia and her pupils were enlarged. Several minutes later she responded to verbal command and Nb latency fell to below the threshold ('three wave' AER) and remained there for almost the entire operation. There were no further meaningful responses of the arm to command although within three minutes of discontinuing the enflurane following delivery her arms moved spontaneously in response to verbal command and she developed a persistent and pronounced tachycardia.

The patient in Fig.10.7. also had raised blood pressure at induction of anaesthesia. Tears were present and pupils were slightly enlarged. She showed no response of any kind (not even spontaneous movement) to verbal command. Before delivery the Nb

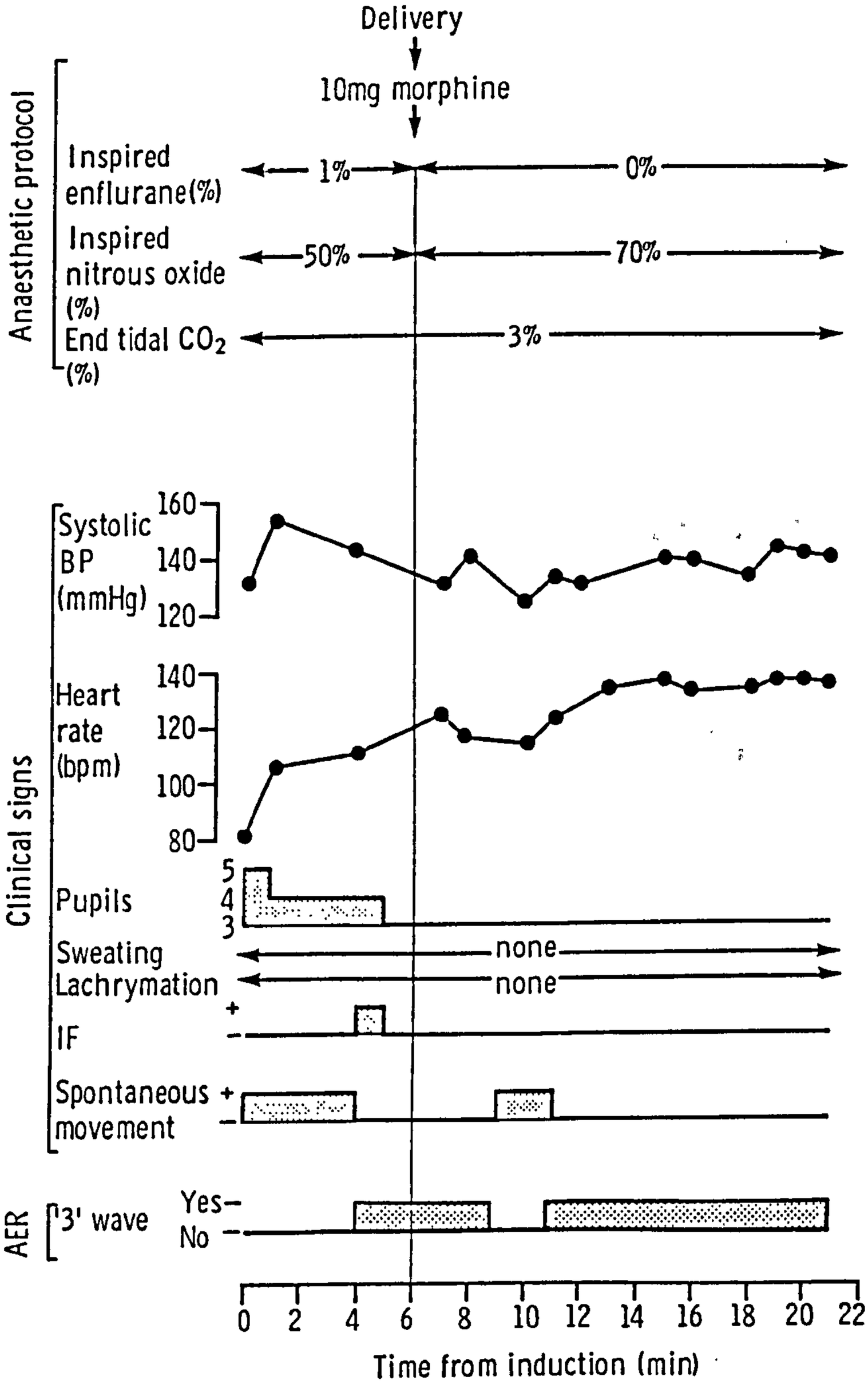


Fig.10.6. Clinical assessment of a patient (Cs5) undergoing Caesarian section. Anaesthetics given, systolic blood pressure, heart rate, presence of sweating, lachrymation, response of isolated forearm (IF) and the AER pattern are shown.

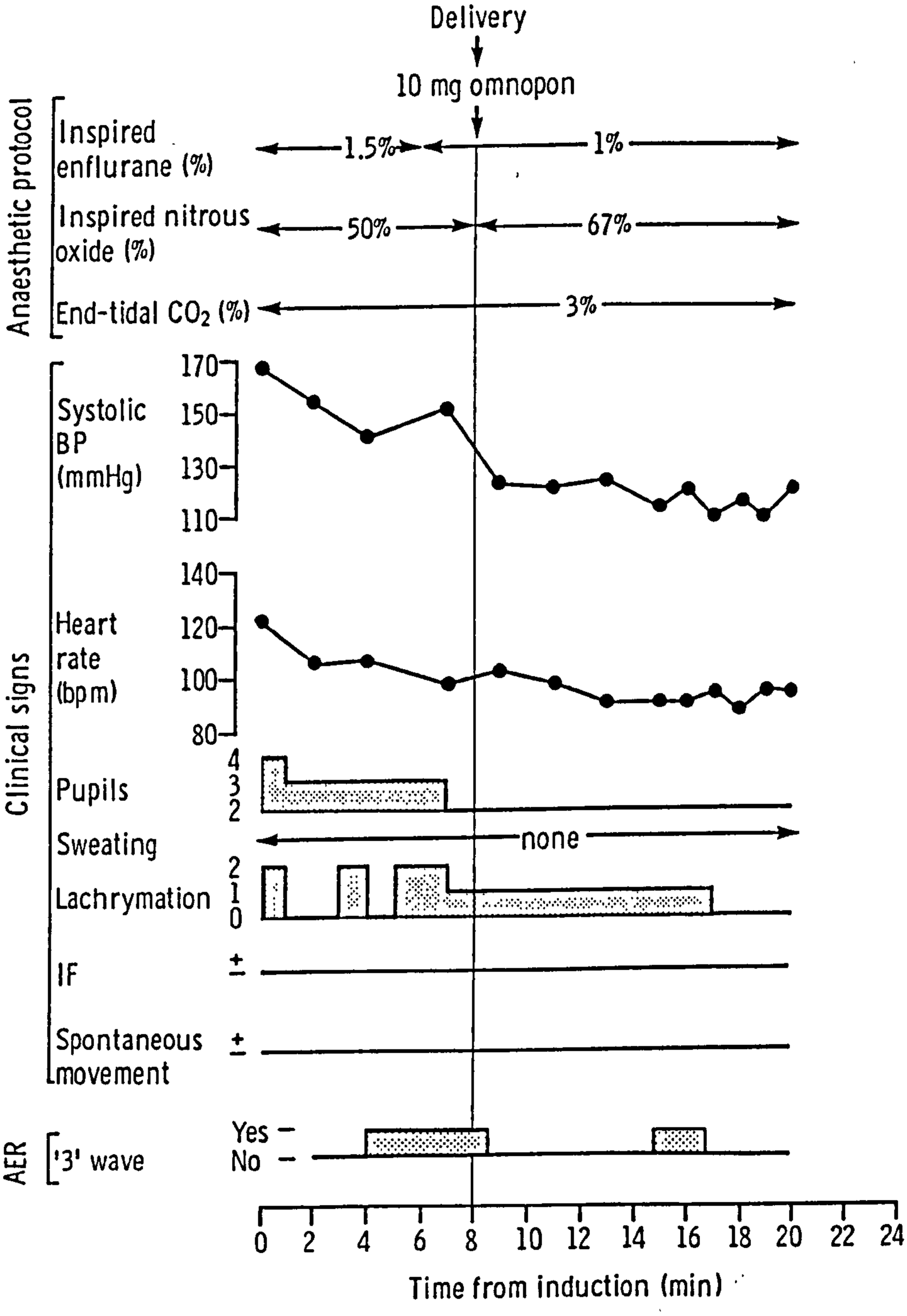


Fig.10.7. Clinical assessment of a patient (Cs6) undergoing Caesarian section. Anaesthetics given, systolic blood pressure, heart rate, presence of sweating, lachrymation, response to isolated forearm (IF) technique and the AER pattern are shown.

latencies were below the threshold ('three wave' AER). After delivery as the enflurane was continued the latencies increased above the threshold ('two wave') with the exception of one datum point.

There were no noticeable differences in the clinical signs of the patients who remained on enflurane following delivery and those in whom it was discontinued. None of the patients in either group had any recall of events when interviewed subsequently.

SECTION D

DISCUSSION

CHAPTER 11

FINDINGS OF THE THESIS

11.1. *Introduction*

The aim of this thesis was to examine the AER for changes that could be used to measure 'depth of anaesthesia'. The requirements, set out in **Chapter 1**, were that the signal should:-

a) be unaffected by neuro-muscular blocking drugs - this has been demonstrated for the early cortical response by Harker et al. in 1977 (see literature review 3.3);
b) indicate 'awareness' or light anaesthesia;
c) show graded changes with increasing concentrations of general anaesthetics;
d) show similar changes with different anaesthetics;
e) show appropriate changes with surgical stimulation.

In this chapter the findings of the thesis are compared with those of other workers in the field and the extent to which the AER fulfills the above criteria is discussed.

11.2. *Graded changes with increasing concentrations of general anaesthetics*

11.2.1. *Brainstem response*

Findings of the thesis : Graded changes in the brainstem response were observed with only three of the six general anaesthetic agents. These were the inhalation agents halothane, enflurane and isoflurane and their effects were to increase the latencies of waves III and V and the interpeak intervals of I-III, I-V and III-V. The fact that the effects of halothane on III latency and I-III interpeak intervals were not significantly different from those of saline is not taken to reflect a fundamental difference between this and the other two inhalation agents. More likely it is due to the smaller magnitude of the effect of this drug in

combination with the small sample sizes. Support for this argument is that III latency was significantly linearly related to halothane concentration.

The three intravenous agents, etomidate, Althesin and propofol, in contrast to the inhalation agents, resembled saline in their lack of effect on the brainstem waves. Neither group of drugs produced consistent changes in I latency or in brainstem amplitudes. (The significant effect of enflurane on V amplitude compared to saline and the significant relationship between V amplitude and enflurane and isoflurane concentration did, however, suggest a trend. If higher concentrations had been used in the investigations more effects on brainstem amplitudes might have been observed.)

The comparison of the effects of the drugs with those of saline was pursued to eliminate suggestions that the observed changes in the brainstem waves were due to residual levels of thiopentone, effects of nitrous oxide on middle ear pressure (Rosenblum, Gal and Ruth, 1982) changing levels of carbon dioxide or decreases in body temperature. These are as likely to occur in the saline group as in the test drug group. Reductions in cerebral blood flow are also unlikely to have contributed to the observed changes as the systolic arterial pressure never fell below 80 mmHg (Lassen and Christensen 1976). The brainstem changes seemed independent of systolic arterial pressure. For instance, propofol and saline produced similar changes in the brainstem response but saline had no effect on systolic arterial pressure whereas propofol substantially lowered it (table 8.7.).

The changes in latency and interpeak interval were linearly related to concentration of the inhalation anaesthetics. (The relationship between the latency of wave III and isoflurane lacked statistical significance but this is more likely to reflect the small sample size than any fundamental difference between isoflurane and the other two inhalation anaesthetics. The slopes against time in Fig.8.5. show an outlier in the isoflurane data. This disappears when III latency is subtracted from V latency but it demonstrates the distortion produced by extreme values in small samples.)

When the estimates of the effects (slopes of the dose response lines) of the three agents were adjusted for anaesthetic potency there were no significant differences between them. The factors mentioned above, i.e. residual levels of thiopentone etc. could contribute to these estimates by making the first datum point, which is an average of responses between five and ten minutes following induction, higher or lower than its real value. In practice the contribution is likely to be negligible. Changes in the brainstem response following thiopentone induction were not detected here or by Dubois et al.(1982b). Brain concentrations of nitrous oxide are approximately 85% equilibrated with inspired concentrations within five minutes and 95% equilibrated within ten minutes of the start of inhalation (Kety and Schmidt 1948; Eger, 1963). Sebel et al. (1984) found 50% nitrous oxide has no effect on the brainstem latencies. The maximum decrease in deep body temperature throughout these studies was 0.5 °C, which would produce changes in I-V, I-III, and III-V interpeak intervals of 0.075, 0.04 and 0.04 ms according to Stockard et al. (1978), or 0.130, 0.07 and 0.06 ms (from 36.5 to 36.0 °C) according to Markand et al. (1987). These would have been constant incremental changes unlikely to affect the estimates of the effects (i.e. the slopes against concentration) of the anaesthetic agents.

The above work was published in a series of papers (see **Appendix**) in the British Journal of Anaesthesia between 1984 and 1987 (Thornton et al. 1984, 1985, 1986 and Heneghan et al. 1987). A definitive paper, using the same analysis as in the thesis to compare the effects of all six anaesthetic agents with saline and with one another, has recently been published (Thornton et al. 1989b). This analysis differs from that in the earlier papers in the following ways:-

1) The effects of each drug (slopes of AER variables against time) are compared with those of saline.
2) Anaesthetic concentrations are converted into units of equipotency and the effects of the drugs (slopes of AER variables against concentration) are compared with one another.
3) The data immediately following induction and intubation (zero time, or zero concentration) are included in this analysis.

3) Mean slopes (calculated from a model which allowed individual patients to have different intercepts and different slopes) are used instead of the common slopes (calculated from a model which fitted parallel slopes but allowed individual patients to have different intercepts), used in the earlier paper.

The reasons for the comparison with saline in this analysis have been given. The disadvantages of using the post-induction datum point as the first point on the slope are discussed above, however, these are outweighed by the advantage of having six data points with which to estimate slopes for individual patients, as opposed the five used in the earlier papers. This is particularly so in the case of the early cortical response, where there were number of possible transformations that could be used to make the data more linear. Mean slopes were used as opposed to common slopes, because on examination of the data from all six drug studies, the earlier parallel slopes model was considered to be an over-simplification. There are small differences in the estimates of the slopes in the thesis compared to the earlier papers, however, the basic conclusions are unaltered.

Work of others : Duncan, Sanders and McCullough (1979) failed to show an effect of halothane on brainstem latencies. Their study was designed to test whether audiometry using evoked responses was valid under halothane anaesthesia. They used unpaired t-tests to compare the data of awake and anaesthetised patients and at various halothane concentrations. An effect of halothane might have been detected if the considerable between-subject variation had been removed using an analysis of variance. Bimar-Blanc, Dejoude and Bimar (1988) studied the effect of increasing concentrations of halothane on I-V interpeak interval and reported similar findings to the ones in the thesis.

Rosenblum, Gal and Ruth (1982) failed to find an effect of enflurane-oxygen anaesthesia on latencies III and V in normal subjects. They argued that the effects of enflurane on the brainstem latencies, which the CRC group reported in 1981 (Thornton et al. 1981) in spontaneously breathing patients, were not due to enflurane but to an exacerbation of conductive hearing loss on

account of increased middle ear pressure caused by nitrous oxide. However, this would not explain the increases in I-V and III-V interpeak intervals reported in 1981 and here. Also the changes in latency and interpeak interval were reversed (although only partially in the period of recovery studied) when enflurane was discontinued and anaesthesia maintained with nitrous oxide and oxygen. Furthermore no such increases in latency and interpeak interval were seen in the 'control' group of patients anaesthetised with nitrous oxide, oxygen and given a saline infusion.

Dubois and et al. (1982a, 1982b) have produced similar findings to those in this thesis with enflurane on III, V latencies and III-V interpeak interval although they found no significant effects on brainstem amplitudes. Sebel et al.(1986), Schmidt and Chraemmer-Jørgensen (1986), Bimar- Blanc et al. (1988), Manninen, Lam and Nicholas (1985) have confirmed the effects of isoflurane on the III, V latencies and interpeak intervals. Unfortunately, most workers do not report end-tidal concentration making quantitative comparisons with their data difficult. However, Sebel et al. (1986) and Schmidt and Chraemmer-Jørgensen (1986) reported the changes in brainstem latencies (ms) with % end-tidal concentration. When re-calculated in ED_{50} units their data give slopes for V latency of 0.28 and 0.29 ms ED_{50} $units^{-1}$ respectively. The agreement is reasonably close to the slope reported here of 0.35 ms ED_{50} $unit^{-1}$ (table 8.3.) considering the small sample sizes and the inevitable differences in methodology between laboratories. Schmidt and Chraemmer-Jørgensen (1986) have confirmed the reduction in V amplitude by isoflurane although their slope of 2.82 μv ED_{50} $units^{-1}$ is considerably larger (also their SEM) than that reported here of 0.02 μv ED_{50} $units^{-1}$ (table 8.4.). Differences in AER recording techniques between laboratories, in particular filter settings, could account for these differences.

With reference to the intravenous agents, Bertoldi et al. (1983) reported a similar lack of effect of etomidate on the brainstem latencies to that reported here. Savoia and his co-workers (1988) have confirmed the results with propofol. They found no effect on waves III and V latencies, I-III, I-V and III- V interpeak intervals or on V amplitude with increasing infusion rates of propofol. Chassard et al. (1989) while presenting data,

which clearly shows an absence of a dose response relationship with propofol, claims that there are significant effects of propofol on brainstem latencies and interpeak intervals. There are no studies on the effect of Althesin on the brainstem components in the literature. However, James (personal communication) has demonstrated that a 3 ml bolus of Althesin increases the latencies of peak V and of the III-V interpeak interval. It is difficult to equate the blood levels achieved here with those reached using a 3 ml bolus. Higher plasma levels of alphaxalone might have produced an effect on the brainstem components had they been used in these studies.

11.2.2. *Early cortical response*

Findings of the thesis : All six of the general anaesthetics studied produced qualitatively similar effects on the early cortical response. These were dose dependent and recovered when the administration of the drug ceased, such that at similar concentrations on ascending or descending drug schedules the appearance of the AER was similar.

The same arguments apply as with the brainstem response, namely that the comparison with the saline data ensures that these are real effects of the anaesthetic agents on the early cortical evoked response, that cannot be dismissed as time-related trends due to residual thiopentone, nitrous oxide etc. However, the estimated effects (slopes against concentration of anaesthetic agent) may have been more affected by these factors than those of the brainstem response.

A carry-over effect of thiopentone to the first datum point (zero drug concentration) is a possible explanation for fact that 11 out of the 36 patients whose data are shown in Table 10.1 showed 'two wave' AER patterns following induction of anaesthesia whereas the other 25 showed 'three wave' patterns. An opposing view is that the 'two wave' pattern is the normal situation in a patient whose anaesthesia is being maintained with 70% nitrous oxide 30% oxygen and the patients that showed the 'three wave' AERs after induction did so as a result of the stimulating effect of tracheal intubation, which takes place during that period. In a recent study carried out by the CRC group (Newton et al. 1989) patients

were given thiopentone for induction of anaesthesia, pancuronium for tracheal intubation and their anaesthesia was maintained with either nitrous oxide or an iso-MAC concentration of isoflurane for three consecutive ten minute periods. It was noted that the amplitudes of the early cortical waves were higher and latencies shorter in the first ten minute period immediately following intubation, compared to the subsequent two ten minute periods which were not different from one another. The stimulating effect of intubation is therefore only likely to affect the first datum point of the slope against concentration. In the case of at least 9 of the patients whose data is shown in Table 10.1. the AERs remained 'three wave' even into the first and sometimes subsequent test periods. Therefore the 'three wave' rather than the 'two wave' AER pattern is most likely to be 'normal' in this situation.

The CRC study also demonstrated that 70% nitrous oxide inspired concentration depressed the early cortical amplitudes and increased their latencies. The fact that equilibration of brain and inspired concentration was not complete could therefore contribute to higher amplitudes and shorter latencies in the first period. These three factors, mentioned above, could make small differences to the estimates of the effects of the general anaesthetic drugs; residual levels of thiopentone by depressing amplitudes and increasing the latencies in the first (zero concentration) period, tracheal intubation and nitrous oxide by tending to reverse this effect.

The same argument concerning body temperature and cerebral blood flow and the brainstem response applies to the early cortical response. A change of 1 ms per 0.5 °C in Pa latency was noted by Kileny et al. (1983) amplitudes were not affected. Spread over a 50 minute period this is unlikely to affect the slope against concentration. Also the early cortical response appeared as robust to changes in systolic arterial pressure as the brainstem response. Etomidate and saline produced similar changes in the systolic arterial pressure but etomidate produced changes in the early cortical waves whereas saline did not.

Comparing the slopes against concentration, expressed in units of equipotency, showed enflurane and isoflurane to be more potent

in their effects on the early cortical latencies and amplitudes than halothane. Enflurane and isoflurane produced approximately a 56% increase in latency and 76% reduction in amplitude compared to halothane which produced a 26% increase in the latencies and 54% reduction in amplitude. Comparing slopes against concentration of the inhalation and intravenous anaesthetics produced large discrepancies between the two groups. The significance of this is discussed in detail in 12.2.3..

The above work was published along with the brainstem data (see Appendix) in the British Journal of Anaesthesia (Thornton et al. 1984, 1985, 1986 and Heneghan et al. 1987). A definitive analysis of the early cortical waves, carried out as in the thesis, has recently been published along with the brainstem data (Thornton et al. 1989b). The differences between this analysis and that of the earlier papers and the reasons for doing the analysis in this way have been explained in the previous paragraphs. An additional difference, which applies only to the early cortical data is that, the amplitudes and latencies have been $\log_e$ transformed. This is because, on examining the plots against time and concentration of *all* 36 patients who were given anaesthetic drugs, this transformation improved the linearity of the fit and made the data more normally distributed. Log_e of the early cortical variables have therefore been used throughout the thesis. The estimated effects of the drugs are now expressed as % change as opposed to ms and μv. This has not altered the conclusions.

Work of others : Studies on the effect of these six general anaesthetics on the early cortical response are few. Celesia and Puletti (1971) recorded from electrodes placed directly on the cortex and found that light halothane/nitrous oxide anaesthesia produced an increase in latency and reduction in the amplitude of peaks which they labelled P1, N1 and P2 and which may correspond to the Po, Na and Pa obtained with scalp recordings. James (personal communication) has demonstrated an increase in latency and a dramatic reduction in amplitude of Pa and Nb following a bolus of 3ml of Althesin. Savoia et al.(1988) have confirmed that increasing propofol infusion rates increase the latencies and decrease the amplitudes of Pa and Nb.

11.3. *Changes reversed by surgical stimulation*

Findings of the thesis :- Increased early cortical amplitudes (waves Pa,Nb, and Pb/Pc were specifically associated with the surgery period in patients in steady state halothane anaesthesia. These were in the opposite direction to the changes produced by halothane. The brainstem and early cortical latencies changed in the same direction as those produced by halothane, that is, they increased. It seemed likely that these latency changes were not specifically related to surgery. A correlation between the effect of surgery on the AER and autonomic changes was not demonstrated in the thesis but the inability to monitor rapid changes could have been responsible for this.

This work was published in the British Journal of Anaesthesia in 1988 (Thornton et al. 1988). However, the early cortical amplitudes and latencies in this analysis have been $\log_e$ transformed, mean changes are now % changes as opposed to ms or μv and there are small differences in the estimates of the effects compared to the early papers.

Work of others :- This is the first demonstration of the effect of surgical stimulation on the AER during controlled anaesthesia. The findings are in keeping with the reported effects of attention and arousal on the cortical sections of the AER, presented in the literature review 4.3.3.. Work carried out by Sebel et al. (1988) on the cortical somatosensory evoked response has shown reversal of the effects of fentanyl/nitrous oxide anaesthesia by the surgical stimulation of skin incision. Reversal of the depressant effects of anaesthetics on the evoked response have been previously reported in animals. Angel and co-workers (1980) showed that the amplitude of the cortical parts of the somatosensory response in rats decreased with increasing anaesthetic concentration. These changes were reversed when ambient pressure was increased. Increasing the ambient pressure also increased the dose of anaesthetic required to prevent reflex response to tail stimulation. Thus the somatosensory evoked response followed pressure reversal of anaesthesia.

Others have shown that surgical stimulation of patients anaesthetised with halothane produced arousal patterns in the EEG, that is, a reduction in amplitude and an increase in frequency (Bimar and Belville, 1977; Oshima, Shingu and Mori, 1981). The increased amplitudes of the early cortical waves seen during the surgical period (described in Chapter 9), were also accompanied by decreased EEG amplitude and increased frequency (Fig.9.2.). It seems likely that the reversal in the amplitudes of the early cortical AER changes by surgical stimulation represents arousal of the CNS.

11.4. *An AER indicator of 'awareness'*

Findings of the thesis : The discriminant analysis produced an easily quantifiable method of deciding if the AER was 'three' or 'two wave' based on whether the latency of the wave Nb was below or above the critical value of 44.5 ms. The clinical studies provided some evidence for an association of the short Nb latencies, i.e. the 'three wave' pattern, and 'awareness' measured using Tunstall's isolated forearm technique (1977). In the investigation prior to general surgery the correlation was good, however, in those during Caesarian section surgery it was less convincing. In the latter patients there were only two clear positive responses to verbal command. There were a number of semi-purposeful movements but not in response to verbal command and these did not appear to be associated with any particular type of AER pattern. On a substantial number of occasions 'three wave' AERs occurred without a response to verbal command. Most of these occurred following the delivery of the infant and furthermore in cases where the enflurane had been turned off (leaving nitrous oxide and morphine to maintain anaesthesia). None of the patients had any spontaneous recall. This has recently been published in the British Journal of Anaesthesia (Thornton et al. 1989a).

Work of others : Some of the studies described in the literature are helpful in interpreting the results although none of them have attempted to do precisely the same thing as here, that is, to correlate changes in the AER with 'awareness'. The literature reports relate to the technical problems associated with the isolated forearm technique. In practice it is difficult to

distinguish between general movement of the arms and a positive isolated forearm response although movement in itself probably indicates discomfort, which must be to some extent related to awareness. Russell (1979) has noted that even when motor nerve stimulation suggests that a volitional response should be possible, patients have reported that they wanted to respond but were incapable of doing so. Millar (1983) has demonstrated that retention of information can take place without overt signs of awareness such as a positive forearm response. In Millar's study the patients in his test group had to identify, from a list, words that had been played to them during their operation. The control group were presented with the same post-operative task but they had been played a tape of radio static during their operations. Although several patients made spontaneous movements of the hand there were no clear positive responses to the isolated forearm technique and no conscious recall. However, the ability to distinguish between target and non-target words was significantly higher in the experimental compared to the control group. This work suggests that there may be an intermediate stage between an overt response to the isolated forearm technique and no response, one in which the patient can 'hear' the request but either is unable to understand it or is insufficiently motivated to respond to it. This is discussed in 12.4. of the next chapter.

CHAPTER 12

SIGNIFICANCE OF FINDINGS

12.1. *Introduction*

In this chapter the significance of the changes in the AER during anaesthesia and surgery are discussed. The association of a particular AER pattern and 'awareness' is examined in the light of current ideas of 'awareness' and 'anaesthesia'.

12.2. *Graded changes with general anaesthetics*

12.2.1. *Brainstem response*

Generator sites along the auditory nerve have been proposed for the brainstem waves, the latency of the wave indicating the speed of arrival at these points (anatomical origins of the brainstem waves are discussed in the literature review 3.4.). The fact that the inhalation agents did not affect wave I latency but increased I-III and III-V interpeak interval suggests that these agents slow transmission from the periphery to the CNS (I-III) and through the brainstem section of the CNS (III-V). Such changes did not occur with the intravenous agents, indicating that depression of activity at these sites is not a pre-requisite for the anaesthetic state. These changes are therefore side effects of general anaesthesia.

12.2.2. *Early cortical response*

In contrast all six general anaesthetics increased the latencies and reduced the amplitude of waves Pa,Nb and Pb, which are thought to originate from the medial geniculate, primary auditory radiation and frontal cortex (anatomical origins of early cortical waves are discussed in the literature review 3.3.), suggesting that depression of the neural activity in these areas may be a pre-requisite for the anaesthetised state. These early cortical changes were not always preceded by changes in the brainstem latencies. When changes in the brainstem and early cortical responses did occur together, recovery of the brainstem response,

on discontinuing the anaesthetic, lagged behind that of the early cortical response. This implies that there are parallel pathways between the auditory receptors to cortical areas, which do not synapse in the brainstem. Some of these may be specifically concerned with arousal, others may not be involved.

12.2.3. *Effects on AER of anaesthetics in relation to their anaesthetic potency*

No difference in the effectiveness of the three inhalation agents in slowing transmission through the brainstem was demonstrated. The MAC values for these agents were used to convert % of end-tidal gas into units of equipotency (ED_{50} units). The concept of MAC is introduced in the literature review **2.6.** and briefly to re-capitulate, it is the minimum alveolar concentration of the anaesthetic which prevents movement to surgical incision in 50% of patients.

When these equipotency conversions were applied to the effects of the inhalation agents on early cortical latencies and amplitudes, halothane was shown to be less potent than enflurane and isoflurane. One posssible explanation for this difference between agents is that the ten minute period allowed for equilibration at each concentration may have been insufficient to ensure that the measured end-tidal concentration reflected brain concentration. On account of their lower solubilities (Eger, 1974) enflurane and isoflurane may equilibrate faster than halothane and hence the discrepancy between estimated and real brain concentration could be less for these agents.

The comparisons between the inhalation and intravenous agents produced enormous differences in their effects on the AER. A number of factors may have contributed to this among them the approximations and assumptions in calculating the equipotent concentrations of inhalation and intravenous agents. The minimum infusion rate (MIR) that prevents movement in response to surgical incision is an attempt to extend the MAC concept to intravenous agents, however the administered dose (infusion rate) does not bear the same close relationship with serum, plasma or blood concentration that the inspired concentration of an inhalation anaesthetic agent does with end-tidal concentration. This is

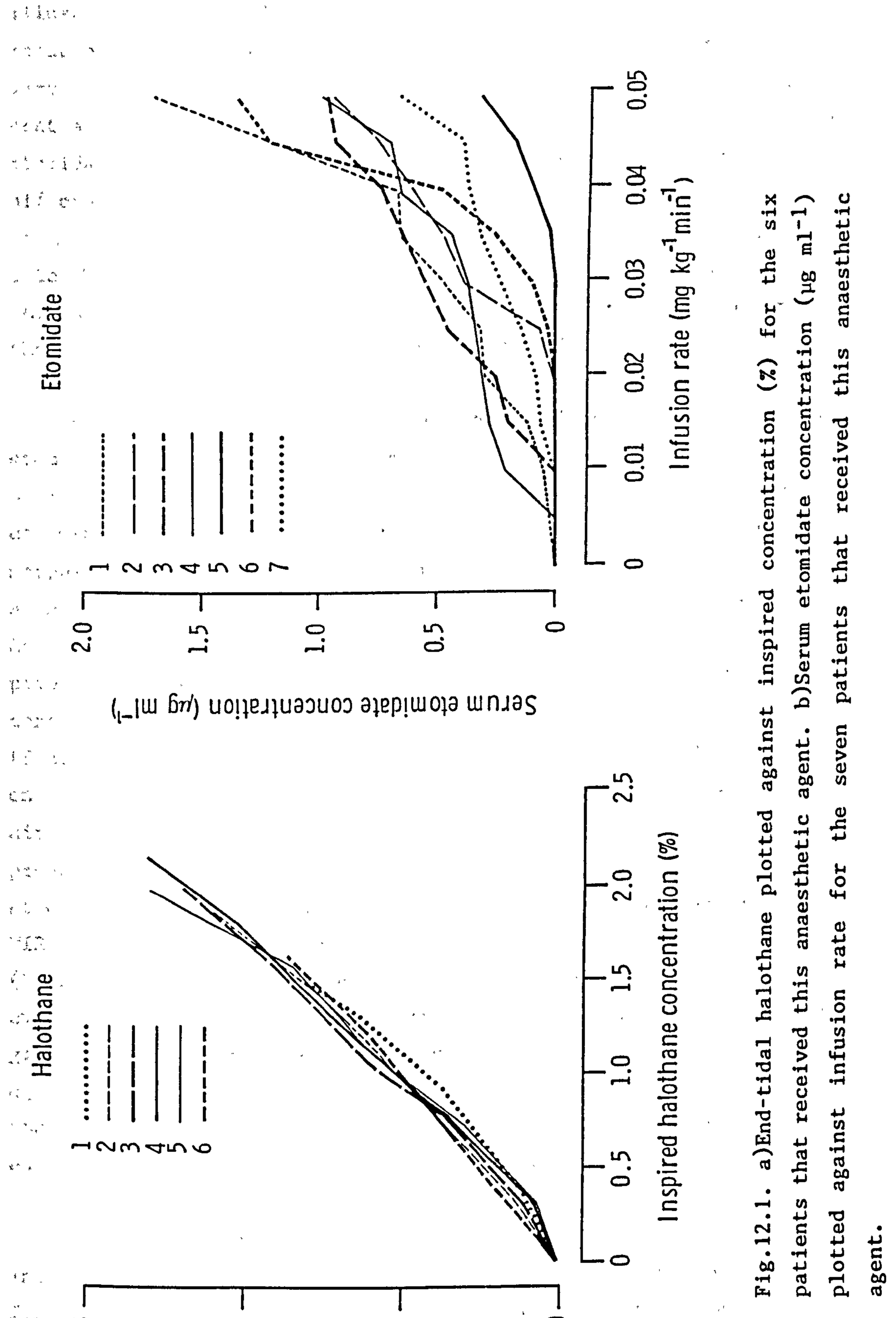


Fig.12.1. a)End-tidal halothane plotted against inspired concentration (%) for the six patients that received this anaesthetic agent. b)Serum etomidate concentration (μg ml⁻¹) plotted against infusion rate for the seven patients that received this anaesthetic agent.

illustrated Fig.12.1. where in the case of halothane the relationship between the inspired and end-tidal concentration was very similar for the six patients that received the drug. In contrast, in spite of the same infusion protocol, the serum etomidate levels in the seven patients given this drug were widely different ranging from 0.32 to 1.7 μg ml^{-1}. In one patient (E7) etomidate was not detected in the serum until the fourth infusion rate had been started. It was in an attempt to reduce the pharmacokinetic variability that the blood drug concentrations at the minimum infusion rate were taken as the ED_{50}s.

To compound these difficulties the minimum infusion rate for etomidate has never been determined and there is only information on minimum infusion rates of propofol and Althesin in the presence of nitrous oxide and in patients previously premedicated with morphine. Nitrous oxide and morphine reduce the MAC of inhalation agents by approximately 83% (Taylor et al.1957; Munson et al.1965). Assuming this is also the case for the intravenous agents the blood propofol concentration of 1.66 μg ml^{-1} and the plasma alphaxalone concentration of 1.91 which correspond to the MIRs for propofol (Sear and Prys-Roberts 1979) and althesin (Spelina et al. 1986) are only contributing 17% to the ED_{50}. By extrapolation, the ED_{50}s in air without morphine premedication would be 9.76 μg ml^{-1} for propofol and 11.23 μg ml^{-1} for alphaxalone. A value of 0.4 μg ml-1 etomidate is estimated as the serum concentration corresponding to MIR, it lying in between the concentration required for surgery (Schüttler et al. 1983; Sear et al. 1984) and that required for hypnosis (Sear 1983). The background drugs (fentanyl and diazepam) given with the etomidate infusion could be considered approximately equivalent to 67% nitrous oxide and 10mg morphine premedication so that the ED_{50} in air, not preceded by any premedication would be estimated at 2.35 μg ml^{-1} serum etomidate.

The discrepancies in the effects of the inhalation and intravenous agents may on the other hand arise for a more fundamental reasons, namely, that the MAC concept and changes in the early cortical AER are reflecting different aspects of anaesthetic function. The predicted changes (calculated from the ED_{50} units) for the effects of the intravenous drugs required extrapolation outside the clinical concentration range, which is

always of debatable validity. For instance, a ninefold increase in latency with Althesin may result in a latency which does not occur in practice. A further example is that the highest blood propofol concentration reached in the study was 4.49 μg ml^{-1} and whereas that for enflurane was 3.14%. At these concentrations, which are considered to be high clinical concentrations in both cases there were similar changes in the early cortical responses for the two anaesthetic agents. However, when the ED_{50} conversions were applied (giving 0.46 ED_{50} units for propofol and 1.87 for enflurane) the predicted differential effects on the AER were enormous.

Drugs such as etomidate, Althesin and propofol have high ED_{50} values probably because they are low in analgesic properties, and the MAC or MAC equivalent end-point, that is the prevention of movement when surgical stimulation is applied, reflects analgesic effects of anaesthetics on the brain as much as their hypnotic effects. Attenuation of the response to surgical stimulation by anaesthetic drugs is complex and there are at least two facets that have to be considered namely (1) reduction of sensory input by the analgesic action of these drugs and (2) abolition of perception by their hypnotic action. These two actions are synergistic in a way that is not understood and may be different for different drugs. It is possible that unlike MAC, the AER reflects mainly the hypnotic effect of an anaesthetic. Clinical experience with propofol administered to patients breathing oxygen (Newton, personal communication) has shown that, while moderate concentrations produce sleep and preclude recall, movement in response to painful stimulus cannot be reliably prevented even when using the highest recommended dose. This may explain why there is only information on MIR for Althesin and propofol in combination with drugs with analgesic properties such as nitrous oxide, morphine and fentanyl, as such supplements are required to achieve this level of anaesthesia.

12.3. *Reversal of general anaesthetic effects by surgical stimulation*

Only the amplitudes of the early cortical waves were affected by surgical stimulation, their latencies and those of the brainstem

waves were not. Surface recordings of the AER sample an envelope of electrical activity. It is generally thought that the amplitude of the response reflects the amount and synchronicity of the neural activity at the generators, whereas the latency, although it depends on this to some extent, mainly reflects the speed of neural transmission. The two things may be independent. Surgical stimulation, which opposed the depression in early cortical amplitudes produced by halothane but not the increases in latency, would appear to increase the absolute amount of neural activity arriving at the cortical sites but not necessarily the speed of transmission. (However, care must be taken in interpreting latencies when the shape of the waveform changes as it does with changes in amplitude.) If the level of arousal of a patient is a balance between the stimulating effects of surgery and the depression of the CNS by general anaesthetic drugs these amplitudes may be reflecting this balance. This seems compatible with the effect of attention or arousal and sleep on these waves (literature review 4.3.3.) in that, the late cortical waves were dramatically affected, early cortical waves changed to some extent brainstem waves were unaffected.

12.4. *An AER indicator of 'awareness'*

12.4.1. *AER variables and 'awareness'*

On practically all occasions when awareness was indicated by a response of the isolated forearm, short Nb latencies suggested a 'three wave' AER. However, the converse was not true. Technical reasons for the occurrence of awareness in the absence of a positive response were examined in 10.4. It has been proposed however, that a distinction should be made between 'responsiveness', which is what the isolated forearm technique measures, and 'awareness'. This distinction may be helpful in understanding the above finding. To pursue this argument, it is first necessary to clarify what is meant by 'awareness' in the context of anaesthesia.

12.4.2. *Definitions of 'awareness' and 'anaesthesia'*

The term 'anaesthesia', introduced by Oliver Wendell Holmes in 1846 (Prys-Roberts, 1987) was an attempt to describe a new phenomenon in a single word. Pinsker (1986) comments that this term is too

non-specific to be of any value to present day medical practice and compares it with those of 'sickness' and 'shock'. However, Prys-Roberts (1987), starting with the essential premise that 'pain' is the conscious perception of a noxious stimulus, defines the state of anaesthesia as that in which, as a result of drug induced unconsciousness the patient neither perceives nor recalls noxious stimulation. But should not 'unconsciousness' take into account perception or recall of the other modalities - auditory, visual, olfactory. If the patient feels no pain but can hear operating theatre conversations surely they cannot be unconscious.

Wilson (1975) has defined awareness as 'the ability of a patient to recall, with or without prompting any event occurring during anaesthesia'. Several methods of prompting have been used such as giving words mixed in a list of non-presented words. On occasions hypnosis has been used to aid recall. However, it is recognised that there may be a further state of awareness, in which a patient has no recall according to any of these methods. Blacher (1984) makes the point that amnesia does not guarantee that the patient was unconsciousness at the time of the operation and does not prevent the consequences of awareness and anxiety that he may have experienced. Bonke et al. (1986) demonstrated that patients, who were subjected to positive suggestions during their operations, took less time to recover than those subjected to white noise or normal operating theatre sounds, although none of the patients had any spontaneous recall of the procedures.

Bennett (1985) looked at what he considers to be an even more sensitive test of awareness that of non-verbal retention to an intra-operative suggestion. During his patients' operations the test group were given the suggestions to 'pull their ear' when visited by the doctor post-operatively. The number of 'ear-pulls' and the time over which these occurred was significantly greater in the test group compared to the control. According to Bennett the patients 'heard' the instructions even though there were no signs (EEG or otherwise) of their having done so at the time. Does this mean that these patients were 'aware'?

On close examination, the data presented in the above studies can be faulted on a number of counts. First, no attempt was made to measure the anaesthetic concentration, and it could be suggested that a proportion of the patients were frankly awake for part of the time. Secondly, many of the reports are anecdotal in that their results fail to achieve statistical significance. Thirdly, the most important factor is the possible bias of the literature, in that negative findings have not been published. At a recent symposium on 'awareness' in Glasgow (April, 1989) papers with negative findings balanced those which supported the concept of intra-operative suggestion. A definitive study with adequate patient numbers and control of anaesthetic variables is yet to be performed.

So far commonsense definitions of 'awareness'and 'anaesthetised' elude anaesthetists, the meaning of these terms depending on the tests used. This arises from the multi-faceted nature of 'awareness' and the problem as Pinsker points out of trying to use one word to express a complex phenomenon. To understand this complex phenomenon Cherkin and Harroun (1971) proposed the 'two-store' theory of memory during anaesthesia.

12.4.3. *'Two-store theory of memory during anaesthesia'*

There are numerous models of memory, none of which are entirely satisfactory. The one proposed by Cherkin and Harroun has the merit of being simple and relating specifically to anaesthesia. In this model, represented in Fig.12.2. information is first perceived then stored in an unstable dynamic form i.e. short term memory. This according to Cherkin and Harroun is what is used to retain a new telephone number when dialing it. Long term memory is used to retain one's own telephone number. In the model, short- term storage may result in intra-operative awareness but not necessarily cause a physiological response i.e. clinical signs, or result in long term storage and subsequent post-operative recall. Narcotic analgesic effects might predominate at the input perception stage. Analgesics are unlikely to affect auditory perception directly but they attenuate the effects of surgical stimulation while anaesthetics and benzodiazepines might act on consolidation.

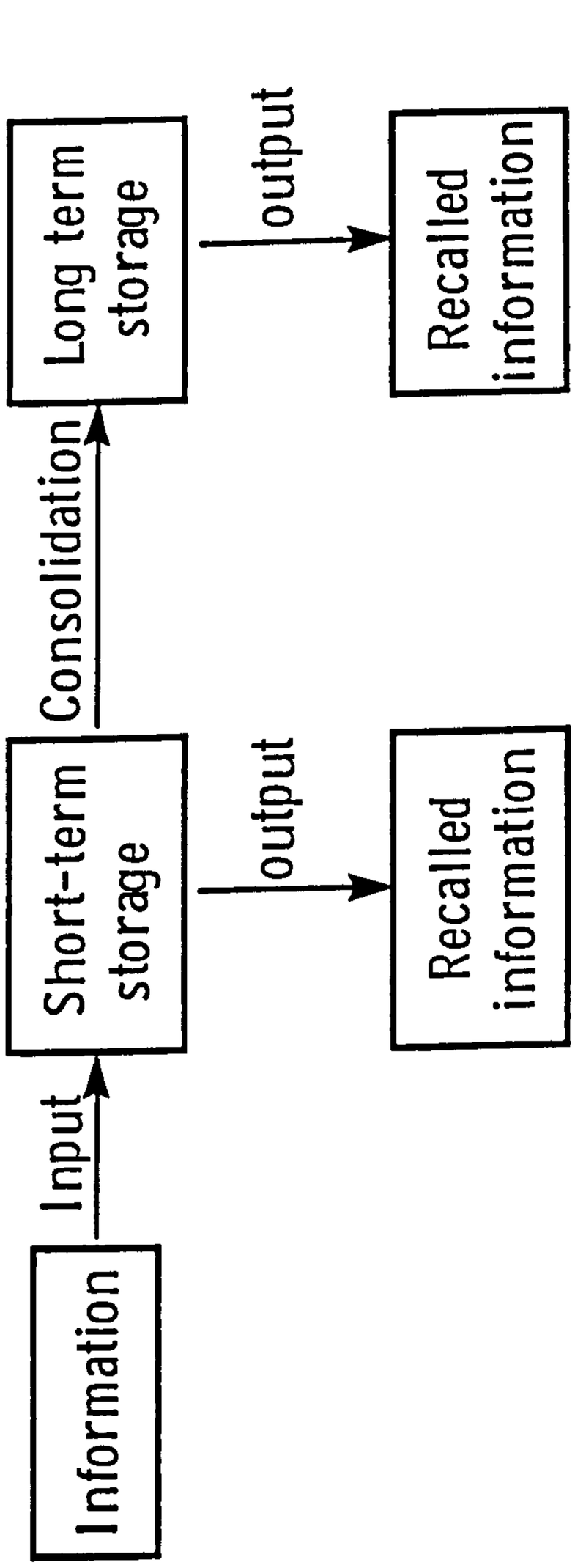


Fig.12.2. Two-store memory model. (Cherkin and Harroun, 1971 Anesthesiology (5) 469-474.)

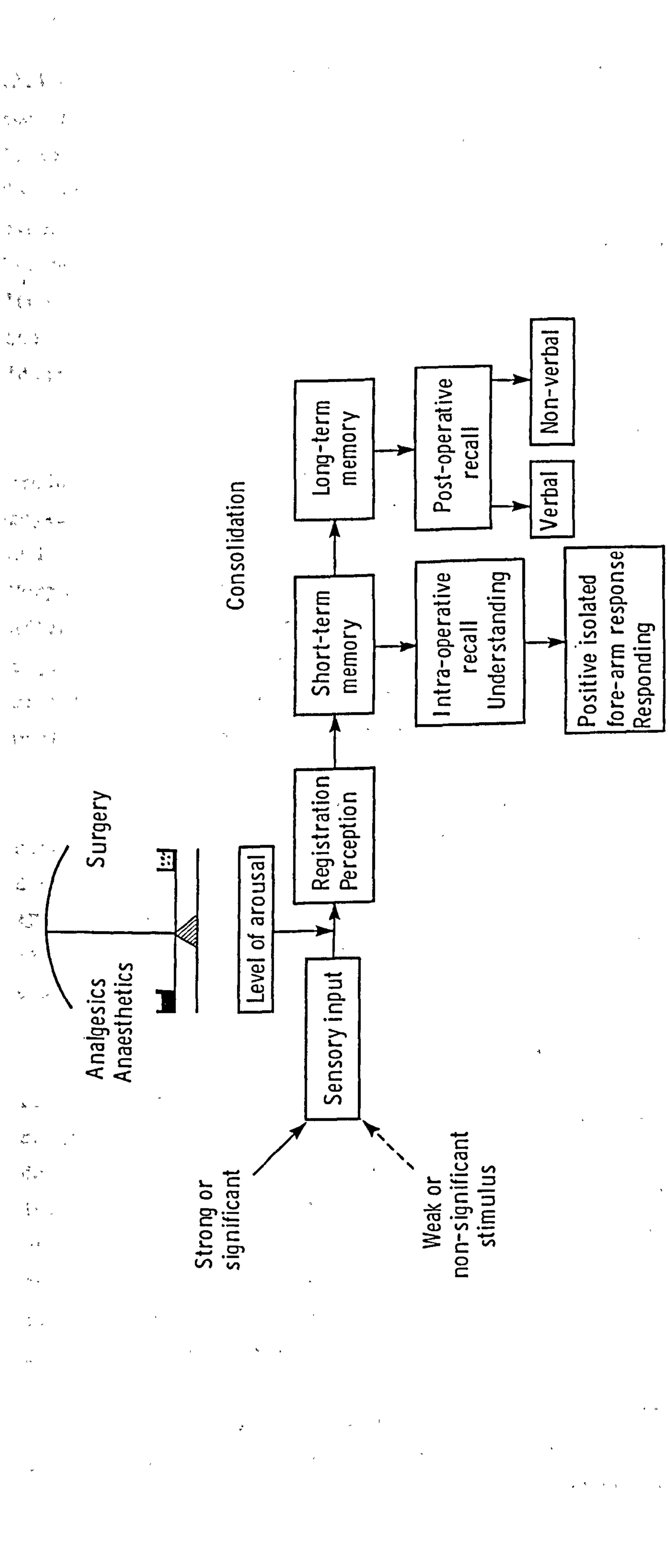


Fig.12.3. Modification of Cherkin and Harroun's model.

12.4.4. *Interpretation of the findings of the thesis in relation to two-store memory model*

Perception or registration of the stimulus : It is proposed that a Nb latency below 44.5 ms indicating a 'three wave' AER is synonymous with perception or registration of the stimulus. Whether this occurs, according to the modified version of the 'two-store' memory theory shown in Fig 12.3., will be influenced by the strength and significance of the stimulus and the patients 'degree of hypnosis'.

General anaesthetic agents such as nitrous oxide and enflurane produce hypnosis and hence reduce the likelihood of the stimulus registering. Surgical stimulation opposes this hypnotic effect and hence increases the likelihood of stimulus registration. Morphine acts synergistically with enflurane in attenuating the effect of surgical stimulation. In the studies in the thesis the registration of the stimulus, a click of a fixed intensity and significance, and the subsequent occurrence of a 'three wave' AER would depend on the balance between these effects.

In the patients studied during anaesthesia prior to general surgery the hypnotic effects of nitrous oxide and enflurane would decrease the likelihood of stimulus registration and a 'three wave' AER pattern. The latter would be most likely to occur when the effects of these two agents were at their lowest and in fact that was the case.

In the patients studied during Caesarian section stimulus registration would depend on the balance between the effects of surgical stimulation, morphine, enflurane and nitrous oxide. Before delivery, the degree of hypnosis would be determined by the interaction between surgical stimulation, enflurane and nitrous oxide. In some patients Nb latencies were below the 44.5 ms threshold i.e. 'three wave' AERs and in some they were above it i.e. 'two wave ' AERs, presumably a reflection of their individual susceptibility to these various agents.

After delivery, the degree of hypnosis would depend on whether the patients were given morphine and nitrous oxide (a weak hypnotic) only, or if this was supplemented with enflurane.

Clearly, in the patients without the enflurane supplement stimulus registration and hence a 'three wave' AER would be more likely. There was in fact a clear distinction in that those without enflurane following delivery had Nb latencies below the threshold ('three wave ' AERs), those with the supplement had Nb latencies that were almost without exception above it ('two wave' AERs).

Positive response of the isolated forearm .· This is not an inevitable outcome of stimulus registration, according to the modified 'two-store' theory in Fig.12.3. Stimulus registration is necessary, however, for a positive forearm response and in these studies virtually all positive responses were accompanied by Nb latencies below the 44.5 ms threshold ('three wave' AERs). For a positive response of the isolated arm, perception of the sound and incorporation into the short-term memory store must have occurred. The motivation to respond to the instructions, however, is also necessary. Experimental subjects given morphine and enflurane in sub-anaesthetic doses report that these drugs interfere with their perception of events and severely influence their motivation to carry out simple instructions. The low incidence of positive responses of the isolated arm, in spite of Nb latencies below 44.5 ms ('three wave' AERs) on a considerable number of occasions' in the patients investigated during Caesarian section surgery, may reflect this situation.

Post-operative recall .· This is not an inevitable outcome of stimulus registration or of a positive response of the forearm, according to the modified 'two-store'theory in Fig.12.3.. Registration of the stimulus, its incorporation into short and long-term memory stores are necessary for the non-specific anxiety syndromes and post-operative recall, whether this occurs spontaneously or is prompted by the various techniques referred to in 12.4.2. This could explain why Nb latencies were on or below 44.5 ms ('three wave' AERs) on many occasions in the post-induction period of the drug studies (25 out of 36, see Table 10.1.) and in the investigations prior to general surgery (24 out 46, see Fig.10.4.) and during Caesarian section (36 out of 70, see Fig.10.5.) in spite of the total lack of post-operative recall in all of these studies.

12.5. *Clinical contribution of the thesis*

The work reported in the thesis shows that the changes in brainstem latencies are not usuable as measures of 'depth of anaesthesia' for 3 reasons:-

a) Although they were affected by the inhalation agents they were not affected by the three intravenous agents in spite of the patients being anaesthetised at the time.

b) The changes were not reversed by surgical stimulation.

c) When the early cortical changes indicated some reversal of anaesthesia the brainstem changes were unaffected.

In contrast, the changes in the early cortical response showed promise as a measure of 'depth of anaesthesia' on account of the following:-

a) The changes were dose dependent.

b) The response showed reversal during recovery from anaesthesia.

c) The changes produced by both the inhalation and intravenous agents were reasonably similar over the clinical concentration range. Discrepancies in the effects of the various anaesthetics and possible reasons for these are discussed at length in 12.2.3..

d) The amplitude changes but not those of latency were reversed by surgical stimulation.

Changes in early cortical amplitude, were not statistically correlated with autonomic changes. This was not unexpected as there is strong evidence that, for the volatile and intravenous anaesthetic agents, autonomic signs of anaesthetic depth are unreliable (**Chapter 1**). This lack of correlation does not invalidate the early cortical amplitudes as a measure of 'depth'.

It is proposed that four stages of 'anaesthetic depth' can be identified using the early cortical response changes shown in a),b), c) and d) of Fig.12.4. which summarises the present findings. The 'three' wave AER (Nb latencies below 44.5 ms) shown in a) indicates inadequate anaesthesia. The 'two' wave AER in b) indicates moderate anaesthesia. The further depression of Pa in c) indicates surgical anaesthesia. During the study on the effect

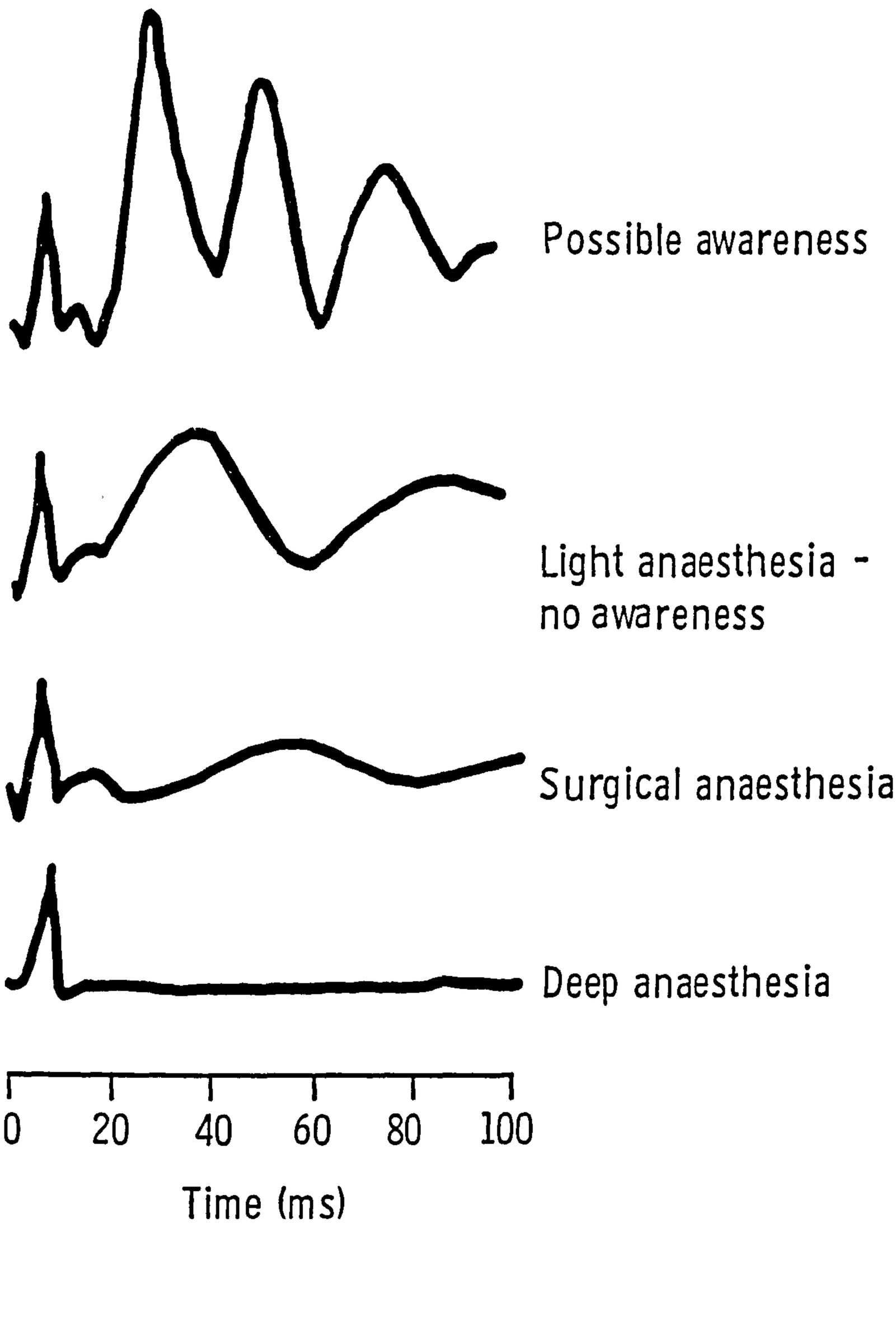


Fig.12.4. The early cortical response in relation to adequacy of anaesthesia.

of surgical stimulation (Chapter 9) patients' AERs showed this amount of depression of Pa and yet did not show unacceptable autonomic signs, however, surgical stimulation may reverse the AER to that in b). The flat early cortical response in d) indicates a deeper level of anaesthesia than is necessary although if the anaesthetic concentration required to produce an early cortical response of this nature does not unduly depress the cardiovascular system then the this amount of depression would indicate that a lack of awareness could be guaranteed.

This is the first demonstration of a graded depression by general anaesthetics and reversal by surgical stimulation, of a CNS response (auditory evoked response) to a stimulus (a click). The EEG is a CNS derived signal but it is not a response to a stimulus. This is an important distinction to make because it is the responsiveness of the CNS that is of interest to the anaesthetist. Cardiovascular measurements, oesophageal contractions, skin conductance etc. are derived from the autonomic as opposed to the central nervous system and as a consequence are affected by the adrenergic and cholinergic drugs used as adjuncts to anaesthesia. The correlation of the 'three wave' to 'two wave' AER transition with response to verbal command also marks the first real progress in the search for an indicator of awareness during anaesthesia. Currently, the work of the thesis represents the nearest approach to a clinically usuable technique for measuring awareness and 'depth of anaesthesia'.

As well as the routine monitoring potential the technique could complement other evoked response (visual and somatosensory) techniques currently used in the operating theatre. The simultaneous use of the AER as a technique for producing a stable anaesthetic, and hence a stable effect on the CNS, would allow the identification of specific changes in the other modalities due to surgical manipulation. In addition, the technique has research application for controlling the 'depth of anaesthesia'.

A limitation of the technique is that it cannot be used in the deaf or those who suffer from neurological disorders. The lack of identifiability of the response in children, reported by some workers (Kraus et al. 1987, Okitsu 1984) also throws into question

its use in children. However, using the filter band pass 25 to 500 Hz, the CRC group had no difficulty in obtaining clear early cortical responses in a 5 year old child once a steady end-tidal anaesthetic concentration was reached and muscle relaxation was achieved. The problems of identification reported by Kraus et al. and Okitsu have been discussed previously in 4.3.2. and may be due to a number of factors. For instance, these workers made no attempt to monitor the level of sedation or stage of sleep. They may on occasions have derived an average from responses associated with different brain states, resulting in a waveform which was not meaningful. Muscle relaxation was not guarenteed in their studies. This may have meant that the early cortical responses were masked by large muscle potentials. In addition their high pass filter settings were too low to ensure adequate rejection of EEG frequencies.

12.6. *Future work*

Clearly further validations of the technique are necessary and studies by the CRC group, which includes the author of the thesis, are in progress and in the planning stage at the present time. Studies which relate the change from 'three to two waves' AER to ability to respond to command and to recall word lists in lightly anaesthetised volunteers have been carried out.

Routine monitoring of the early cortical AER in a large group of patients in the operating theatre are being carried out. It is planned to relate the changes in the AER to the severity of surgical stimulation and the anaesthetist's impression of the patients' 'depth'. Having obtained a data bank of AERs from patients at different depths a computerised method for analysing the waveforms will be developed.

The possibility that the early cortical AER may primarily measure only the hypnotic aspect of anaesthesia needs to be addressed. Studies on the effects of nitrous oxide and isoflurane on the cortical somatosensory evoked response (SER) have shown these components to be more profoundly affected by nitrous oxide than would be expected from the relative anaesthetic potencies of these drugs (McPherson et al. 1985). The cortical SER is also

severely depressed by drugs, such as fentanyl and morphine (Pathak et al. 1984), which are not anaesthetics. In contrast to the early cortical auditory evoked response the somatosensory evoked response components may be measuring the analgesic aspect of anaesthesia. To test this hypothesis a study, to examine the somatosensory evoked response alongside the auditory evoked response, is proposed.

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APPENDIX

Publications from the thesis